

Appendix A
U.S. Patent No. 10/551,475

Claims (Presented in February 17, 2009 Amendment)	Support in Present Application ¹	Support in Priority UK Application (UK patent 0307559.5)
<p>47. (currently amended). Library comprising a plurality of tagged ligands of formula I</p> $(Lig J_L)_m L (J_r Tag)_m (J_r L (J_L Lig)_m)_p$ <p>and salts thereof wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers</p> <p>comprising one or a plurality of same or different ligand moieties Lig each linked to one or a plurality of same or different tag moieties Tag via same or different linker moieties L and same or different linking site or linking functionality J_r and J_L</p> <p>wherein Lig comprises a GPCR ligand, an inhibitor of an intracellular enzyme or a substrate or inhibitor of a drug transporter;</p> <p>L is selected from a <u>single</u> or double bond, -O-, -S-, amine, COO-, amide, -NN-hydrazine; and saturated or unsaturated, substituted or unsubstituted C₁₋₆₀₀ branched</p>	<p>[0014]</p> <p>[0173]</p> <p>[0014]</p> <p>[0045]</p>	

¹ Support for present application is shown by citations to paragraph numbers in U.S. Publication No. 2006/0122045 A1

<p>or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, wherein optional substituents are selected from any C₁₋₂₀ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano and carbonyl and combinations thereof, and L may be monomeric, oligomeric having oligomeric repeat of 2 to 30 or polymeric having polymeric repeat in excess of 30 up to 300;</p>		
<p>Tag is any tagging substrate;</p>	[0015]	
<p>m are each independently selected from a whole number integer from 1 to 3;</p>	[0016]	
<p>p is 0 to 3</p>	[0017]	
<p>wherein one or more of each -Tag in one or more or each library compound is a fluorophore entity</p>	[0018]	
<p>-Fl, whereby the library comprises compounds of which one or more or all of which are of formula</p>	[0027]	
<p>I'</p>		
<p>(LigL)_m L (J_TFl)_m (J_LLig)_m)_p</p>		
<p>characterised in that linking is at same or different linking sites in compounds comprising different Lig, J_L, L J_T and/or - Tag and is at different linking sites in compounds comprising same Lig, J_L, L J_T and/or - Tag</p>	[0018]	
<p>wherein the or each Fl is selected from a red, near ir or blue dye with the proviso that when Lig is</p>	[0015]	
<p>CGP12177 and L is 1,1,4,4 tetramethyl butylamine C(CH₃)₂(CH₂)₂C(CH₃)₂NH, Fl is not BODIPY@FL, or when L is C(CH₃)₂(CH₂)₂C(CH₃)₂NHCSNH then Fl is not FITC, eosin or erythresin.</p>		

48. (withdrawn and currently amended)	Library comprising a plurality of tagged ligands of formula I	
	$(\text{Lig J}_L)_m \text{ L } (\text{J}_T \text{ Tag})_m (\text{J}_T \text{ L } (\text{J}_L \text{ Lig})_m)_p$	[0014]
and salts thereof wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers		[0173]
comprising one or a plurality of same or different ligand moieties Lig each linked to one or a plurality of same or different tag moieties Tag via same or different linker moieties L and same or different linking site or linking functionality J _T and J _L		[0014]
wherein Lig comprises a GPCR ligand, an inhibitor of an intracellular enzyme or a substrate or inhibitor of a drug transporter;		
L is selected from a <u>single or double bond</u> , -O-, -S-, amine, COO-, amide, -NN-hydrazine; and saturated or unsaturated, substituted or unsubstituted C ₁₋₆₀₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, wherein optional substituents are selected from any C ₁₋₂₀ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano and carbonyl and	[0045]	

	combinations thereof, and L may be monomeric, oligomeric having oligomeric repeat of 2 to 30 or polymeric having polymeric repeat in excess of 30 up to 300;	[0015]	
	Tag is any tagging substrate;	[0016]	
	m are each independently selected from a whole number integer from 1 to 3;	[0017]	
	p is 0 to 3	[0018]	
	wherein one or more of each -Tag in one or more or each library compound is a fluorophore entity -Fl, whereby the library comprises compounds of which one or more or all of which are of formula	[0027]	
	I'		
	$(Lig)_m L (J_T Fl)_m (J_T L (J_L Lig)_m)_p$		
	characterised in that linking is at same or different linking sites in compounds comprising different Lig, J_L , L , J_T and/or -Tag and is at different linking sites in compounds comprising same Lig, J_L , L , J_T and/or -Tag.	[0018]	
	wherein the or each Fl is selected from the following dyes: Texas red™, coumarin and derivatives, Cascade Blue™, EvovBlue and fluorescent derivatives thereof, pyrenes and pyridyloxazole derivatives, the cyanine dyes, the dyomics (DY dyes and ATTO dyes) and fluorescent derivatives thereof, the Alexafluor dyes and derivatives, BDI dyes including the commercially available Bodipy™ dyes, pyrenes, anthracenes, acridines, fluorescent phycobiliproteins and their conjugates and fluoresceinated microbeads, and Texas Red derivatives, coupled to amine groups using the isocyanate, succinimidyl ester or dichlorotriazinyl-reactive groups.	[0115]	
49	(withdrawn and currently amended). Library as claimed in any of Claim 47 wherein each	[0028]	

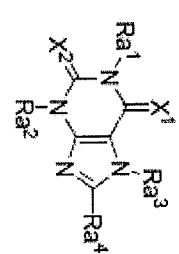
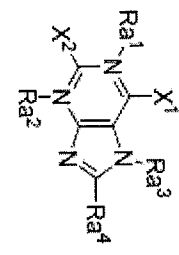
<p>compound of formula I or I' comprises one of a plurality of fluorophores and/or tags providing a library of differently fluorescently tagged ligands comprising one or a number of different fluorophores optionally of different chemical composition or spectral characteristics; and/or providing a library of differently tagged ligands including at least one fluorescently tagged ligand; [0030]alternatively each compound of formula I or I' comprises one of a plurality of precursor ligands linked each to one or a plurality of different tags providing a library of same or differently tagged ligands of plural ligand type; alternatively each compound of formula I comprises one of a plurality of linkers linking a precursor ligand and at least one Tag at the same or different linking site; alternatively each compound of formula I or I' comprises the same linker linking a precursor ligand and at least one Tag at different linking sites providing a library of differently linked tagged ligands of different conformation or anticipated pharmacology and binding.</p>		
<p>50 (withdrawn). Library as claimed in Claim 47 comprising a plurality of compounds of one or more of formula II to III:</p> <p>II (LigJ)_m L J_r TagJ_r L (J_L Lig)_m where each m is as hereinbefore defined and is preferably 1 or 2, more preferably 1</p> <p>III (LigJ)_m L (J_rTag)_m wherein each m is as hereinbefore defined and is preferably 1 and/or 2, more preferably</p> <p>Lig J_L – L – J_L Tag and/or</p> <p>Lig J_L – L – J_r Tag and/or Lig J_L – L – J_r Tag</p>	[0030]	

J _L Lig	J _T Tag		
wherein each J _L and J _T comprises J as hereinbefore defined and may be same or different and may derive from functionality originally present in Lig or L and Tag or L or a combination thereof, characterised in that linking is at same or different linking sites in compounds comprising different Lig, J _L , L, J _T and/or Tag, and is at different linking sites in the case of any two or more compounds comprising identical Lig, J _L , L, J _T and/or Tag.			
51 (withdrawn). Library as claimed in Claim 47 including information for each compound of formula I comprised in the Library, relating to the pharmacology for binding to or inhibition of a GPCR receptor or to inhibition of an intracellular cyclic nucleotide phosphodiesterase, or inhibition of or transport by a drug transporter including designation as agonist, antagonist, substrate or inhibitor and measure of affinity or inhibition, enabling quantification of results.	[0036; lines 7-14]		
52 (withdrawn). Library as claimed in Claim 47 wherein a GPCR ligand is selected from any compound which is effective as an agonist or antagonist for an adenosine receptor, a beta-adrenoceptor, a muscarinic receptor, a histamine receptor, an opiate receptor, a cannabinoid receptor, a chemokine receptor, an alpha-adrenoceptor, a GABA receptor, a prostanoid receptor, a 5-HT (serotonin) receptor, an excitatory aminoacid receptor (glutamate), a dopamine receptor, a protease-activating receptor, a neurokinin receptor, an angiotensin receptor, an oxytocin receptor, a	[0021]		

<p>leukotriene receptor, a nucleotide receptor (purines and pyrimidines), a calcium-sensing receptor, a thyroid-stimulating hormone receptor, a neurotensin receptor, a vasopressin receptor, an olfactory receptor, a nucleobase receptor (adenosine), a lysophosphatidic acid receptor, a sphingolipid receptor, a tyramine receptor (trace amines), a free-fatty acid receptor and a cyclic nucleotide receptor; an inhibitor of intracellular enzymes is an inhibitor of cyclic nucleotide phosphodiesterases; and a substrate or inhibitor of a drug transporter is selected from a substrate or inhibitor of an equilibrium based drug transporter or ATP driven pump selected from a catecholamine transporter, a nucleoside transporter, an ATP-binding cassette transporter, a cyclic nucleotide transporter or derivatives or analogues thereof ;</p> <p>or wherein Lig is selected from</p> <p>a) xanthine like structures including XAC, theophylline, caffeine, theobromine, dyphilline, enprofylline; or fused biaryl structures including papaverine, dihydroquinilones, cilostamide, dipyridamole or vinpocetine; and analogues thereof;</p> <p>b) adenosine like structures including ADAC, NECA and analogues thereof;</p> <p>c) ethanolamine like structures including salmeterol, salbutamol, terbutaline, quinprenaline, labetalol, sotalol, bambuterol, fenoterol, reproterolol, tulobuterol, clenbuterol and analogues thereof;</p> <p>d) oxypropanolamine like structures including CGP12177, propranolol, practolol, acebutalol, betaxolol, ICI 118551, alprenolol, celiprolol (celectol), metoprolol (betaloc), CGP20712A, atenolol, bisoprolol, misaprolol, carvedilol, bucindolol, esmolol, nadolol, nebivolol, oxprenolol, xamoterol, pindolol, timolol and analogues thereof;</p> <p>e) xanthine like structures including XAC, theophylline, caffeine, theobromine, dyphilline,</p>	<p>[0022]</p> <p>[0023; lines 9-13]</p> <p>[0038]</p> <p>[0039]</p> <p>[0040]</p>	
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<p>enprofylline, sildenafil, EHNA (erythro-9-(2-hydroxyl-3-nonyl)adenine), zaprinast, or spiro bicyclic structures including bypyridines, amrinone; imidazoles, C1930; dihydropyridazinones, indolan, rolipram, SB207499; or fused biaryl structures including papaverine, dihydroquinilones, ciliostamide, dipyridamole, vimpocetine and analogues thereof.</p>	[0041]	
<p>53 (withdrawn). Library as claimed in Claim 47 wherein J_m L J_m comprises a mono, di, tri, tetra, penta, or hexa amino, alkylthio, alkoxy, carboxylic acid, and combinations thereof including a mono, di or tri aminoalkylthio, amino alkoxy, alkoxy carboxylic acid or alkoxy amine, mono, di or tri amino menthane, amino ethane, thio ethane, ethane, amino acyl, polypeptide, or mono or polyether derivatives including diamine or dithio derivatives, mono or polyethylene glycol di or tri amine or thio; or comprises a mono-, di-, tri- or tetra, penta or hexafunctional linear or branched or cyclic substituted or unsubstituted hydrocarbyl of formula -L.L-</p> <p>J [A] q_L R_L [A' q_L, J']_p A' q_L, J''</p> <p>wherein each of J to J'' is a linking site or functionality as hereinbefore defined independently selected from a single or double bond, methylene, alkyne, alkene, NR, O, CONR, NRCO, S, CO, NCO, CHHal and P wherein R is H or C₁₋₈ alkyl or cycloalkyl or forms part of a cyclic ring with N, Hal is any halogen selected from chlorine, iodine, bromine; and is present in any rational</p>	[0049] [0050]	

<p>location in a group A to A'';</p> <p>each of A to A'' is a group selected from -O-, -C(=O)-, C₁₋₁₂ alkoxy, alkoyl, cycloalkyl, heterocyclic, alkyl, alkenyl, aryl, arylamide, arylamine, amino, thioalkyl, heteroaryl as hereinbefore defined and combinations thereof, optionally substituted by groups selected independently from C₁₋₃ alkyl and C₁₋₅ alkoxy;</p> <p>each of q_L to q_L' are independently-selected from 0 or 1 or indicates an oligomeric repeat and is from 2 to 30, or indicates a polymeric repeat unit and is from 31 up to 300.</p> <p>R_L is a C, N or S atom or is a CR_L, NR_L, alkyl, cycloalkyl, heterocyclic, aryl heteroaryl, amine or thio moiety and provides for branching when p is 1 or 2; wherein R_L is H or C₁₋₃ alkyl; and</p> <p>p is as hereinbefore defined and is 0, 1 or 2.</p>		
<p>54. (withdrawn). Library as claimed in Claim 47 wherein J_m L J_m is of formula</p> <p>J Aq_L R_L J''</p> <p>wherein each of J and J'' is amine or -O-, A is CH₂CH₂O, q_L is 1-30 or 31 to 300 and R_L is CH₂CH₂</p> <p>or of formula</p> <p>J Aq_L R_L(A'J') J''</p> <p>wherein each of J, J' and J'' independently is amine, -O or a single bond, q_L is 1, 2 or 3 -30 or 31 to 300 and A is CH₂CH₂O or HNCH₂CO or q_L is 1 and A is C(O) or (CH₂)₁₋₈ or q_L is 0, R_L is CH or CH₂CH, q_L' is 0 or q_L' is 1 and A' is CH₂ and q_L' is 0</p>	[0059]	

<p>preferably</p> <p>$O(CH_2CH_2O)_{q_L}CH_2CH_2NH, O(CH_2CH_2O)_{q_L}CH_2CH(CH_2NH)NH,$</p> <p>$OCH(CH_2NH)NH, -CH(CH_2NH)NH, -C(O)NH-, -(CH_2)_{1-8}$ or $(-HNCH_2CO-)_{1-3}$ (= -gly₁₋₃-) -.</p>	
<p>55. (withdrawn). Library as claimed in Claim 47 wherein each compound of formula I or I' comprises a moiety Lig and L as hereinbelow defined:</p> <p>Wherein:</p> <p>any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers</p>	<p>[0060]</p> <p>[0173]</p>
<p>Lig._{4m} is suitably of the formula, in either of the following forms given, including any of its possible linking configurations or sites:</p>	<p>[0061]</p>
<div style="text-align: center;">   </div>	<p>[0062]</p>

<p>Lig.a¹_m</p>	<p>[0063] [0064] [0065]</p>	
<p>Wherein</p> <p>at least one or all of Ra¹ to Ra⁴, X¹ and X² comprise a linking site or functionality J as hereinbefore defined</p> <p>X¹ and X² are each independently selected from H, O, OR.a, NR.a, NHR.a;</p> <p>X¹ and X² are each preferably O;</p> <p>each of R.a¹, R.a², R.a³ and R.a⁴ independently is selected from H or C₁₋₄ linear or branched alkyl optionally mono or multi hydroxy or halo substituted;</p>	<p>[0066]</p>	
<p>R.a⁴ is selected from a heteroatom O, S or substituted or unsubstituted amine or saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo and cyano; including optionally substituted aryl, cycloalkyl, alkyl, ketone, (di)amine, (di)amide, alkoxy, cycloalkyl, carboxylic acid or optionally o-, m- or p- substituted phenyl wherein substituents include aryl,</p>	<p>[0067]</p>	

alkyl, cycloalkyl, heteroaryl or heteroalkyl, amine, amide, carboxyl, carbonyl or $R.a^4$ comprises cyclohexyl, cyclopentyl, ethoxy, $(CH_2)_2PhPh$, CH_2Ph , $CONH(CH_2)_nCONH$, $CH_2CONH(CH_2)_2NH$, $CH_2PhNHCOCH_2$, $CH_2CH_2OCOCH_2$, succinimidyl ester, $NHCOCH_2$, $CH_2(CH_3)NCOCH_2$, $H_2N(CH_2)_2NHCOCH_2$, $H_2N(CH_2)_8NHCOCH_2$, $H_2NNHCOCH_2$, $CH_2CONH(CH_2)_2NHCOCH_2$, $HOPhCH_2N(CH_2CH_3.HOAc)(CH_2)_2NHCOCH_2$, heterocyclic- $(CH_2)_4CONH(CH_2)_2NHCOCH_2$ or heterocyclic- $NHCON(heterocyclic)COCH_2$;

or Lig a is of the formula Lig.a²-



wherein at least one or all of $R.a^5$ to $R.a^6$, or a cyclic C or heteroatom comprise a linking site or functionality J as hereinbefore defined, each of $C.A1$ and $C.A2$ is independently selected from C_{5-6} aryl, heteroaryl, cycloalkyl and heterocyclic, more preferably from phenyl, or aryl containing 1 or 2 ring heteroatoms, or heterocyclic containing 1 ring heteroatom and/or 1 ring $-C=C-$ group;

Each of up to seven $R.a^5$ is a substituent of a ring carbon or a ring heteroatom and:

is independently selected from H, halo, hydroxy, thiol, amine, $COOH$, hydrazine, cyano, saturated or unsaturated, substituted or unsubstituted C_{1-20} branched or straight chain

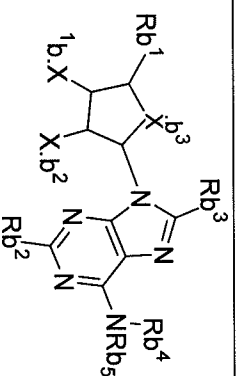
[0068]

[0069]

[0070]

[0071]

<p>aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, and wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo =O or cyano; OCH₃, CH₂Ph(OCH₃)₂, O(CH₂)₃CON(CH₃)c.hex, N(CH₂CH₂OH)₂, c.hex, COOCH₂CH₃, CH₂CH₃;</p> <p>or any two or more of R.a⁵ form a one, two or three ring fused cyclic structure, a fused 3 ring aryl, 5-heterocyclic or 6-heterocyclic structure having 4 ring atoms common with the fused bicyclic Lig.a² structure;</p> <p>and R.a⁶ is a moiety as defined for R.a⁵ above;</p>	
<p>and L.a is as hereinbefore defined for L or J_L L J_T or L.I or subformulae as hereinbefore defined, or is a single bond, amino acid or amide including a peptide or polypeptide gly or gly₃, alkyl of formula -(CH₂)_n where n is 3 to 8, optionally including one or more heteroatoms or unsaturated groups, including -O- or -S- or -CH=CH-;</p>	<p>[0072]</p>
<p>Lig.b is suitably of the formula Lig.b including any of its possible linking configurations or sites:</p>	<p>[0073]</p>



wherein at least one or all of Rb¹ to Rb⁵ or Xb¹ to Xb³ comprise a linking site or functionality J as hereinbefore defined

[0074]

ring substituents X.b¹ and X.b² are independently selected from hydrocarbon including alkyl or SR_X, NR_{X,2} and OR_X wherein (each) R_X is selected from H, C₁₋₃-alkyl, alkenyl; ring heteroatom X.b³ is selected from -S-, -O- and -CH₂-;

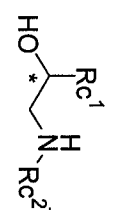
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[0076]

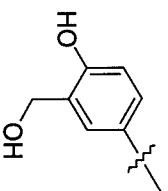
Rb¹ is selected from saturated or unsaturated, substituted or unsubstituted C₁₋₄ aliphatic, or C₁₋₃ alicyclic optionally including one or more heteroatoms N, O, S, P, wherein substituent(s) are selected from one or more cycloalkyl, heterocyclic, hydroxy, oxo, halo, amine; or R.b¹ comprises a carbonyl substituted by H, alkyl or a linear or cyclic primary, secondary or tertiary amine, substituted C₁₋₃ alkyl, cycloalkyl or amide, cyclopropyl, or CONHC₁₋₃alkyl including CONHEt or CH₂OH and each of R.b² and R.b³ is selected from H, halo, hydroxy, thiol, amine, COOH, CHO, hydrazine, cyano or saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as

[0077]

[0078]

<p>hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo or cyano, preferably from H, halo or hydroxy;</p> <p>Rb⁴ is H;</p> <p>Rb⁵ is H or alkyl</p> <p>L.b comprises a linking site or functionality J as hereinbefore defined; and is as hereinbefore defined for L or its subformulae, more preferably is saturated and unsaturated substituted or unsubstituted C₁₋₁₂ aliphatic or C₁₋₂₄ aromatic as defined for L optionally including one or more heteroatoms O, S or N, cyclic or heterocyclic groups, or is of formula L.I or its subformulae as hereinbefore defined, or is (CH₂)_m wherein m is 2 to 12, or is (Ph-CH₂CONH)₂ (CH₂)₂;</p> <p>Lig.c is of the formula Lig.c including any of its possible linking configurations or sites:</p> <p>Lig.c HOC*(R.c¹)CH₂NH-R.c²</p> <div style="text-align: center;">  </div> <p>where at least one or all of R.c¹ to R.c² or OH, or a chain C or N comprise a linking site or functionality J as hereinbefore defined</p> <p>* indicates an optically active centre and</p> <p>wherein R.c¹ is C₆₋₁₄ aryl optionally including one or more heteroatoms selected from H, O,</p>	<p>[0079]</p> <p>[0080]</p> <p>[0081]</p> <p>[0082]</p>	
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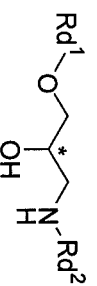
optionally substituted by OH, Hal, NH₂, NHC₁₋₃alkyl, sulphonamide, oxoamine or (-CONH₂), or is mono, di or tri substituted phenyl or quinoline wherein substituents include OH, Cl or NH₂, or is m-CH₂OH, p-OH phenyl, m-,p-dihydroxy phenol or m-,m-dihydroxyphenol, m-,m-diCl, p-NH₂ phenol, p-OH, m-CONH₂ phenol or 5-OH, 8-quinoline,



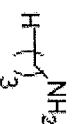
R.c² is selected from saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any optionally substituted C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amino, hydrazine, oxo or cyano and combinations thereof; or R.c² is selected from C₁₋₆ branched or straight chain aliphatic, C₆₋₁₀ araliphatic optionally substituted by OH and optionally including heteroatoms selected from N,O, optionally including an ether O, and is selected from -(CH₂)₆OCH((CH₂)₃Ph), CHCH₃(CH₂)₂Ph, CHCH₃CH₂PhOH,

[0086]

[0087]



C(CH₃)₂CH₂Ph or from the structures:



L.c is present as R.c² or comprises a linking site or functionality J as hereinbefore defined, and is as hereinbefore defined for L, formula L.I or its subformulae as hereinbefore defined, or is selected from C₁₋₁₂ alkyl, amide;

[0088]

Lig.d is of the formula Lig.d including any of its possible linking configurations or sites:

Lig.d R.d¹ OCH₂C*HOHCH₂NH-R.d²

where at least one or all of Rd¹ to Rd² or OH, a chain C or N comprise a linking site or functionality J as hereinbefore defined

[0089]

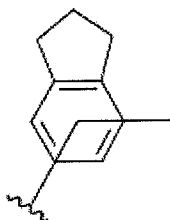
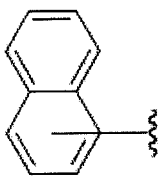
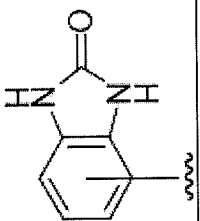
* indicates an optically active centre

wherein R.d¹ is saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional

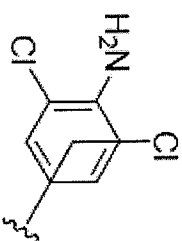
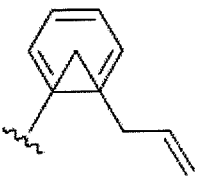
[0090]
[0091]

substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo or cyano; or R.^d is substituted or unsubstituted C₁₋₂₄ aralkyl or heteroaralkyl, including single ring and fused ring systems with (hetero)aryl or cycloalkyl rings, wherein optional substituents include C₁₋₆ alkyl, alkoxy, ether, carbonyl, alkenyl, amine, amide each optionally carbonyl, amide, halo or OH substituted, or halo or OH, amine, amide, carbonyl, ketone, ether substituted phenyl or naphthyl, mono-, di-, tri- or tetra substituted mono or polycyclic fused aryl or cycloaryl or heterocycloaryl including phenyl, carbazole or structures shown below or spiro ring systems, mono-, di-, tri- or tetra alkoxyalkyl, alkoxyalkoxyalkyl or CF₃ substituted phenyl or unsubstituted or monosubstituted naphthalene or 5,6 ring systems:

[0092]



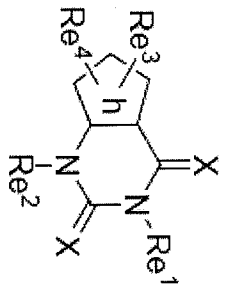
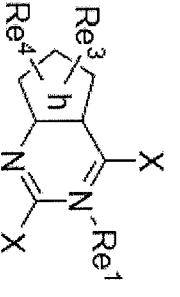
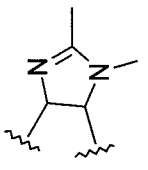
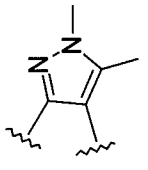
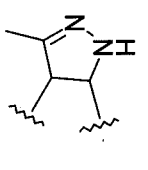
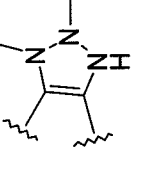
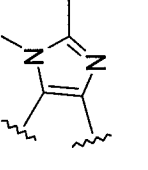
[0092]

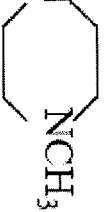


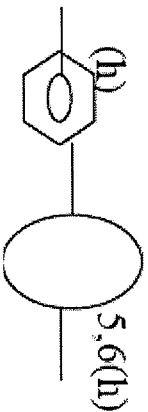

R,d²

is substituted or unsubstituted amine, saturated or unsaturated, substituted or unsubstituted C₁₋₁₂ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo or cyano, more preferably amine, C₁₋₆ branched or straight chain alkyl optionally including ether O, and optionally substituted by C₆₋₁₀ aryl, or of the formula:

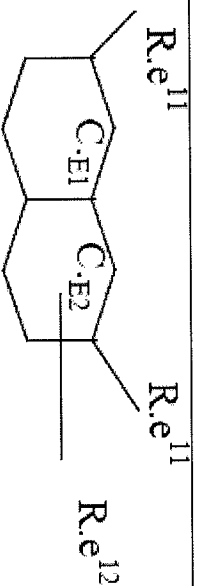
<p>L.d</p> <p>may be present as R.d² or may comprise a linking site or functionality J as hereinbefore defined and is as hereinbefore defined for L and its subformulae , formula L.I and its subformulae as hereinbefore defined, or is a single bond or is as hereinbefore defined for L.a;</p> <p>Lig.e¹</p> <p>Lig.e comprises a cell permeant moiety or is associated with a cell permeant L or FI moiety or is of the formula , in either of the following forms given including any of its possible linking configurations or sites:</p> <div data-bbox="1088 231 1429 1218"> </div>	<p>[0094]</p>

<p>wherein</p> <p>at least one or all of Re^1 to Re^4, X and a ring C or N comprise a linking site or functionality J as hereinbefore defined</p> <p>h is selected from</p> <div style="display: flex; justify-content: space-around; align-items: center;">   </div> <div style="display: flex; justify-content: space-around; align-items: center;">    </div> <div style="display: flex; justify-content: space-around; align-items: center;">   </div> <p>each optionally substituted by $\text{R.e}^3 - \text{R.e}^4$ wherein $\text{R.e}^1 - \text{R.e}^4$ are as $\text{R.a}^1 - \text{R.a}^4$ defined above or in which R.e^3 is C_{5-9} linear or branched alkyl, optionally mono or multi hydroxy or halo substituted or is aryl optionally substituted by alkoxy or</p>	<div style="display: flex; justify-content: space-between;"> <div style="text-align: right;"> <p>[0095]</p> <p>[0096]</p> </div> <div style="text-align: left;"> <p>[0097]</p> </div> </div>
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<p>sulfonyl,</p> <p>ortho-OEt, meta-SO₂N</p>  <p>NCH₃</p> <p>each X is independently selected from H, O, -OR.e², N, HN, NR.e⁵, HR.e⁶, and aryl optionally substituted by ether; or X is aryl optionally alkyl or alkoxy substituted or is Ph-ortho-OCH₂CH₂CH₃;</p> <p>and where R.e⁵ is as defined above for R.e¹ above or forms a fused cyclic ring together with the adjacent ring N atom, or 1 or 2 fused 5 membered cyclic rings;</p> <p>and R.e⁶ is as defined above for R.e¹ above or is selected from optionally substituted phenyl wherein optional substituents include ether, o-ethoxy or o-propoxy, alkyl or OH, sulphonyl or carbonyl substituted by heterocyclic, or cyclic C₅₋₈ alkyl, piperazinyl or sulphonyl;</p> <p>or Lig.e is of the formula Lig.e²</p>	<p>[0098]</p> <p>[0099]</p> <p>[0100]</p>
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<p>Lig.e²</p> <p>wherein</p> <p>at least one or all free ring atom or their substituents comprise a linking site or functionality J as hereinbefore defined</p> <p>each spiro ring optionally comprises zero or one or more heteroatoms h</p> <p>or</p> <p>(h)  5,6(h)</p> <p>comprises zero or 1 N</p> <p>heteroatom and  5,6(h) comprises zero, 1 or 2 N heteroatoms and is unsaturated or comprises one or two -C=C- or -C=N- groups; and wherein each ring is optionally substituted by one or more oxo, CO, COOH, C₁₋₆ alkyl or linear or cyclic alkoxy optionally substituted by one or more oxo, CO, COOH, CN, or C₁₋₆ alicyclic or amine groups, amine or one or more spiro or fused heterocycles;</p> <p>or Lig.e is of the formula Lig.e³</p>	<p>[0101]</p> <p>[0102]</p> <p>[0103]</p> <p>[0104]</p>
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Lig.e³



wherein at least one or all of Re¹¹ to Re¹², or a ring C or heteroatom or ring substituent comprise a linking site or functionality J as hereinbefore defined

[0105]

each of C.E1 and C.E2 is independently selected from C₅₋₆ aryl, heteroaryl, cycloalkyl and heterocyclic, including phenyl, or aryl containing 1 or 2 ring heteroatoms, or heterocyclic containing 1 ring heteroatom and/or 1 ring -C=C- group;

[0106]

each of up to seven R.e¹¹ is a substituent of a ring carbon or a ring heteroatom and:

[0107]

is independently selected from saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, and wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo =O, or cyano, OCH₃, CH₂Ph(OCH₃)₂,

[0108]

electrophilic group.		
58. Canceled		
<p>59. (withdrawn and currently amended). Process for the preparation of a library as claimed in ef Claim 47 which is a combinatorial process; and comprises the reaction of one or more ligand precursors of formula IV and/or IV'</p> <p>IV $(\text{LigI})_m - \text{L} - \text{Y}_{\text{Lm}}$</p> <p>IV' $\text{Lig Y}_{\text{Ligm}}$</p> <p>comprising one or more or different reactive groups Y_{L} or Y_{Lig} forming a linking functionality J, J_{L} or J_{r} as hereinbefore defined</p> <p>with one or more of a plurality of analytical tagging substrates of formula V and/or V'</p> <p>V $\text{Y}_{\text{Tm}} \text{Tag}$</p> <p>V' $\text{Y}_{\text{Tm}} \text{L} (\text{J}_{\text{r}} \text{Tag})_m$</p> <p>comprising one or more or different reactive groups Y_{r} forming a linking functionality J or J_{r} as hereinbefore defined</p> <p>and optionally one or more linking species VI or VI' or VI''</p> <p>VI $\text{Y}_{\text{Lm}} \text{L} \text{Y}_{\text{Lm}}$</p> <p>wherein Lig, J, L, J_{r} and Tag and each m is independently as hereinbefore defined</p>	[0132]	

<p>wherein the or each compound of formula IV or IV' is capable of reaction with the or each compound of formula V or V', optionally via the or each species VI or VI' or VI'' to form a plurality of compounds of formula I as hereinbefore defined;</p> <p>wherein linking is at same or different reactive sites in different compounds as hereinbefore defined.</p>		
<p>60 (withdrawn and currently amended). Process for the preparation of a compound of formula I as hereinbefore <u>hereinbelow</u> defined in Claim 47-64 comprising the reaction of a compound of formula IV or IV' and a compound of formula V or V' and optionally additionally VI, as hereinbefore defined in <u>claim 59</u>, by reacting the unprotected primary alkyl amine group of a compound of formula IV with a compound of formula V comprising a reactive succinimide ester group in solvent at ambient temperature without the need for subsequent deprotection.</p>	[0142]	
<p>61-62 (canceled).</p>		
<p>63 (withdrawn and currently amended). Method <u>Process</u> as claimed in Claim 62 <u>59</u> which <u>comprises additionally determining pharmacology for a plurality of or all compounds in the library in order to enable selecting a compound exhibiting desired pharmacology, whereby the process comprises preparing a preliminary library of compounds, conducting screens to assess binding or</u></p>	[0154, line 6-8] [0155]	

<p>inhibition, selecting a compound identified in the screen as having beneficial properties, and modifying or functionalising by nature of moieties or linking location of linking on the basis of the indications from the screen to prepare an optimised library, wherein the molecular pharmacology and photochemistry from the screen feedback into the design of the library.</p>		
<p>64. (currently amended). A compound of formula I</p> $(Lig\ J_L)_m\ L\ (J_T\ Tag)_m\ (J_T\ L\ (J_L\ Lig)_m)_p$ <p>or salt thereof wherein an optically active ligand is present as a racemate or as one of its optically active isomers</p> <p>comprising ligand moiety <u>Lig</u> linked to tag moiety <u>Tag</u> via linker moiety <u>L</u> at linking site or linking functionality <u>J_T</u> and <u>J_L</u></p> <p>wherein <u>Lig</u> comprises a GPCR ligand, an inhibitor of an intracellular enzyme or a substrate or inhibitor of a drug transporter;</p> <p><u>L</u> is selected from a single or double bond, -O-, -S-, amine, COO-, amide, -NN-hydrazine; and saturated or unsaturated, substituted or unsubstituted C₁₋₆₀₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, wherein optional substituents are selected from any C₁₋₂₀ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore</p>	<p>[0159]</p> <p>[0173]</p> <p>[0114]</p> <p>[0045]</p>	

<p>defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano and carbonyl and combinations thereof, and L may be monomeric, oligomeric having oligomeric repeat of 2 to 30 or polymeric having polymeric repeat in excess of 30 up to 300; m are each independently selected from a whole number integer from 1 to 3; p is 0 to 3</p> <p>wherein -Tag is a fluorophore entity -Fl, whereby the compound is of formula I'</p> $(\text{LigL})_m \text{L} (\text{J}_1\text{Fl})_m (\text{J}_1\text{L}) (\text{J}_1\text{Lig})_{m/p}$ <p>characterised in that Fl is selected from a red, near ir or blue dye with the proviso that:</p> <p>a) when Lig is XAC ie in Lig a when each of R.a¹ and R.a² is propyl, R.a³ is H and R.a⁴ is -Ph-OCH₂CONH(CH₂)₂NH-, and L is a single bond Fl is not BODIPY™ 630/650 X; or</p> <p>b) when Lig is ABEA, ie m is 4 and L is a single bond Fl is not BODIPY™ 630/650 X, as hereinbefore defined in Claim 47 wherein J_m-L-T_m is of formula</p> $\text{J} \text{Aq}_L \text{R}_L (\text{A}'\text{J}')_{j'} \text{J}'$ <p>wherein each of J and J' is amine or O-, A is -CH₂CH₂O-, q_L is 1-30 or 31 to 300 and R_L is -CH₂CH₂ or of formula</p> $\text{J} \text{Aq}_L \text{R}_L (\text{A}'\text{J}')_{j'} \text{J}'$ <p>wherein each of J, J' and J'' independently is amine, O or a single bond, q_L is 1, 2 or 3-30 or 31 to 300 and A is -CH₂CH₂O- or -HNCH₂CO- or q_L is 1 and A is C(O) or (CH₂)₁₋₈ or q_L is 0, R_L is -CH or -CH₂CH-, q_L is 0 or q_L is 1 and A' is -CH₂ and q_L is 0</p>	<p>[0015]</p> <p>[0017]</p> <p>[0018]</p> <p>[0027]</p> <p>[0115]</p> <p>[0170]</p> <p>[0171]</p>	
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preferably $O(CH_2CH_2O)_{q_1}CH_2CH_2NH_2, O(CH_2CH_2O)_{q_1}CH_2CH(CH_2NH_2)NH_2,$ $OCH(CH_2NH_2)NH_2, CH(CH_2NH_2)NH_2, C(O)NH_2, (CH_2)_{1-8} \text{ or } (HNCH_2CO)_{1-3} (= \text{gly}_{1-3}) \text{ and}$ wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers.		
<p>65. (currently amended). A compound of formula I as defined in Claim 64 which is a compound of formula II or III as hereinbefore defined in Claim 50</p> <p>II $(Lig)_m L J_T Tag J_L (J_L Lig)_m$ where each m is as hereinbefore defined and is preferably 1 or 2, more preferably 1</p> <p>III $(Lig)_m L (J_T Tag)_m$ wherein each m is as hereinbefore defined and is preferably 1 and/or 2, more preferably</p> <p>$Lig J_L - L - J_L Tag$ and/or</p> <p>$Lig J_L - L - J_T Tag$ and/or</p> <p>$J_L Lig$ $J_T Tag$</p> <p>$Lig J_L - L - J_T Tag$ and wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers.</p>	[0030]	

<p>66. (currently amended). A compound according to Claim 64, wherein <u>Fl</u> is of formula <u>J_T-t-</u><u>Fl</u> and comprises a BODIPY™ structure characterised by a dipyrrometheneboron difluoride core, optionally modified by one or two fused rings, optionally substituted by one or several substituents selected from alkyl, alkoxy, aryl or heterocyclic, wherein one substituent -t- is adapted for linking as hereinbefore defined to a ligand precursor as hereinbefore defined, wherein the substituent -t- comprises a proximal unsaturated or aryl moiety, comprising a medial short, medium or long chain alkynyl or cycloalkyl moiety and comprising a moiety derived from linking via a reactive group as hereinbefore defined or selected from carboxyl, sulphonate or as a heteroatom O or S or methylene derived from linking at an alkylhalide including methylbromide, haloacetamide or sulphonate ester electrophilic group, Lig comprises a GPCR ligand, an inhibitor of an intracellular enzyme or a substrate or inhibitor of a drug transporter or Fl is a fluorophore entity, with the proviso that when Lig is CGP12177 and L is 1,1,4,4-tetramethyl butylamine $C(CH_3)_2(CH_2)_2C(CH_3)_2NH$, Fl is not BODIPY@Fl, or when L is $C(CH_3)_2(CH_2)_2C(CH_3)_2NHCSNH$ then Fl is not FITC, eosin or erythrosin</p> <p>characterised in that the or each Fl is selected from a red, near ir or blue absorbing dye or from BODIPY@630/650 or BODIPY@630/650 X.</p>	<p>[0118]</p> <p>[0120; line 9-end]</p>	
<p>67. (currently amended). A compound of the formula I or I' as hereinbefore defined in Claim 56-55 selected from formulae Lig.a_m L.a-Fl.a_n to Lig.e_m L.eFl.e_n as hereinbefore defined with the proviso that:</p>	<p>[0159]</p>	

<p>a) when Lig is XAC ie in Lig a when each of R.a¹ and R.a² is propyl, R.a³ is H and R.a⁴ is Ph OCH₂CONH(CH₂)₂NH, and L is a single bond or L is gly and n=3 or L is NCS, Fl is not fluorescein; or</p> <p>when Lig is XAC and L is a single bond or NCS, Fl is not fluorescein or NBD;</p> <p>b) when Lig is adenosine Fl is not Fmoc (CA 134:204756); or</p> <p>when Lig is ADAC, ie R.b¹ is CH₂OH, R.b² and R.b³ are H and L is (Ph CH₂CONH)₂(CH₂)₂ or L is a single bond, Fl is not fluorescein, NBD or Rhodamine; or</p> <p>when Lig is NECA (incorporating the moiety (CH₂)_m) ie R.b² and R.b³ are H and L is a single bond, or is (CH₂)_m when m is 2,4,6,8 or 10 then Fl is not NBD, or when m is 3,4,6,8,10 or 12 then Fl is not dansyl; or</p> <p>when Lig is N⁶-[2-(4-aminophenyl)ethyl]adenosine and L is (CH₂)₂PhNH, Fl is not FITC (CA 131:56155 (8))</p> <p>e) when Lig is CGP12177 and L (R.d²) is mono amine menthane, Fl is not BODIPY® TMR; or</p> <p>when Lig is CGP12177 and L is 1,1,4,4-tetramethyl butylamine, ie C(CH₃)₂(CH₂)₂C(CH₃)₂NH Fl is not BODIPY® FL, or when L is C(CH₃)₂(CH₂)₂C(CH₃)₂NHCSNH then Fl is not FITC, eosin or erythrosin; or when L is monoamine menthane, Fl is not FITC (CA 131:56155 (4)); or</p> <p>when Lig is CGP12177 and L is a single bond, Fl is not NBD; or</p> <p>when Lig is alprenolol ie o-prop-2-enyl phenyl and L is C(CH₃)₂ or a single bond, Fl is not NBD;</p> <p>and a) e) when L is a single bond, Fl is not BODIPY FL;</p>	
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<p><u>optionally additionally</u></p> <p>a) when Lig is XAC ie in Lig a when each of R.a¹ and R.a² is propyl, R.a³ is H and R.a⁴ is -Ph-OCH₂CONH(CH₂)₂NH-, and L is a single bond FI is not BODIPY™ 630/650 X; or</p> <p>b) when Lig is ABEA, ie m is 4 and L is a single bond FI is not BODIPY™ 630/650 X.</p>	<p>[0170] [0171]</p>	
<p>68. (currently amended). A compound of the formula I</p> $\text{(Lig J}_L\text{)}_m \text{ L (J}_T\text{ Tag)}_m \text{ (J}_T\text{ L (J}_L\text{ Lig)}_m\text{)}_p$ <p>or salt thereof and salts thereof wherein an optically active ligand is present as a racemate or as one of its optically active isomers</p> <p><u>comprising ligand moiety Lig linked to tag moiety Tag via linker moiety L at linking site or linking functionality J_T and J_L</u></p> <p><u>wherein Lig comprises a GPCR ligand, an inhibitor of an intracellular enzyme or a substrate or inhibitor of a drug transporter;</u></p> <p><u>L is selected from a single or double bond, -O-, -S-, amine, COO-, amide, -NN-hydrazine; and saturated or unsaturated, substituted or unsubstituted C₁₋₆₀₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, wherein</u></p>	<p>[0159] [0173] [0114] [0045]</p>	

<p>optional substituents are selected from any C₁₋₂₀ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano and carbonyl and combinations thereof, and L may be monomeric, oligomeric having oligomeric repeat of 2 to 30 or polymeric having polymeric repeat in excess of 30 up to 300;</p> <p>m are each independently selected from a whole number integer from 1 to 3;</p> <p>p _____ is 0 to 3</p> <p>wherein -Tag is a fluorophore entity -Fl, whereby the compound is of formula I'</p> $(\text{LigL})_m \text{L} (\text{J}_T \text{Fl})_m (\text{J}_T \text{L} (\text{J}_1 \text{Lig})_m)_p$ <p>Lig, J_T, L, J_T, Fl as defined in claim 47</p> <p>wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers</p> <p>wherein Fl is a fluorophore as hereinbefore defined and is selected from the class of dyes in particular including fluorescein, fluorescein derivatives including FITC, and fluorescein-like molecules including Oregon Green™ and its derivatives, Texas red™, 7-nitrobenz-2-oxa-1,3-diazole (NBD) and derivatives thereof, coumarin and derivatives, naphthalene including derivatives of dansyl chloride or its analogues or derivatives, Cascade Blue™, EvoBlue and fluorescent derivatives thereof, pyrenes and pyridyloxazole derivatives, the cyanine dyes, the dyomics (DY dyes and ATTO dyes) and fluorescent derivatives thereof, the Alexafluor dyes and derivatives, BDI dyes including the commercially available Bodipy™ dyes, erythrosin, eosin, pyrenes, anthracenes, acridines, fluorescent phycobiliproteins and their conjugates and</p>	<p>[0015]</p> <p>[0017]</p> <p>[0018]</p> <p>[0027]</p> <p>[0115]</p>	
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<p>fluoresceinated microbeads, Rhodamine and fluorescent derivatives thereof including Rhodamine Green™ including the tetramethylrhodamines, X-rhodamines and Texas Red derivatives, and Rhodol Green™, coupled to amine groups using the isocyanate, succinimidyl ester or dichlorotriazinyl-reactive groups, and</p> <p>wherein Lig-J_E-L-J_F is selected from:</p> <p>xanthine like structures</p> <p>adenosine like structures;</p> <p>ethanolamine like structures; and</p> <p>oxypropanolamine like structures; wherein</p> <p>linking functionality-J_F is amine; and</p> <p>wherein linker L is selected from branched and straight chain C₁₋₅₀ alkyl, C₆₋₅₀ cycloalkyl or aryl and combinations thereof optionally comprising one or more heteroatoms O and optionally substituted by C₁₋₁₂ aliphatic, or for xanthine like structures L is also selected from a single bond,</p> <p>with the proviso that when Lig is XAC ie in Lig.a when each of R.a¹ and R.a² is propyl, R.a³ is H and R.a⁴ is -Ph-OCH₂CONH(CH₂)₂NH-, and L is a single bond Fl is not BODIPY™ 630/650 X; or</p> <p>b) when Lig is ABEA, ie m is 4 and L is a single bond Fl is not BODIPY™ 630/650 X.</p>	<p>[0170]</p> <p>[0171]</p>	
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<p>69 (withdrawn). A kit comprising a Compound of formula I or I' as hereinbefore defined in Claim 47 associated with information relating to its pharmacological properties in the form of Spectral Properties given as Excitation Max and Emission Max, Fluorescence Lifetime and Emission quantum yield and Pharmacology defined in terms of cells expressing a GPCR receptor as hereinbefore defined or expressing an intracellular cyclic nucleotide phosphodiesterase, or a drug transporter as hereinbefore defined and given as the Inhibition or Antagonism of receptor binding or of receptor functionality together with a value for the Inhibition (pK_B) or Antagonism (pK_i) binding constants, and optionally together with fluorescent images of the pharmacological binding in single living cells illustrating the defined inhibition or antagonism, preferably the pharmacological properties are given as EC_{50} values for agonist stimulated – or pK_i values for antagonism of agonist stimulated second messenger generation, or substrate K_m values or antagonist K_i values for stimulation or inhibition of intracellular enzymes or drug transporters.</p>	<p>[0157]</p>	<p>[0158, lines 17-21]</p>

<p>70 (currently amended). Compound of formula IV or IV' or library thereof as hereinbefore defined in Claim 59 useful for linking to any suitable tag of formula V or V' as hereinbefore defined in Claim 59;</p> <p>wherein the linker moiety is of formula</p> $J-Aq_E-R_E(J')_E-J''$ <p>wherein each of J and J' is amine or O, A is $\text{CH}_2\text{CH}_2\text{O}$, q_E is 1-30 or 31 to 300 and R_E is CH_2CH_2</p> <p>or of formula</p> $J-Aq_E-R_E(A'J')_E-J''$ <p>wherein each of J, J' and J'' independently is amine, O or a single bond, q_E is 1, 2 or 3-30 or 31 to 300 and A is $\text{CH}_2\text{CH}_2\text{O}$ or HNCH_2CO or q_E is 1 and A is $\text{C}(\text{O})$ or $(\text{CH}_2)_{1-8}$ or q_E is 0, R_E is CH or CH_2CH, q_E is 0 or q_E is 1 and A' is CH_2 and q_E is 0</p> <p>preferably</p> $\text{O}(\text{CH}_2\text{CH}_2\text{O})_{q_E}\text{CH}_2\text{CH}_2\text{NH}_2, \text{O}(\text{CH}_2\text{CH}_2\text{O})_{q_E}\text{CH}_2\text{CH}(\text{CH}_2\text{NH}_2)\text{NH}_2,$ $\text{OCH}(\text{CH}_2\text{NH}_2)\text{NH}_2, \text{CH}(\text{CH}_2\text{NH}_2)\text{NH}_2, \text{C}(\text{O})\text{NH}_2, (\text{CH}_2)_{1-8} \text{ or } (\text{HNCH}_2\text{CO})_{1-3} (= \text{gly}_{1-3})-$	[0179]	
<p>71 (withdrawn and currently amended). Fluorophore linker of formula V' or library thereof as</p>	[0180]	

<p>hereinbefore defined in Claim 59 wherein the linker moiety is of formula</p> $J-Aq_L-R_E-J''$ <p>wherein each of J and J'' is amine or O, A is $-CH_2CH_2O-$, q_L is 1-30 or 31 to 300 and R_E is $-CH_2CH_2-$</p> <p>or of formula</p> $J-Aq_L-R_E(A'J'')_n-J''$ <p>wherein each of J, J' and J'' independently is amine, O or a single bond, q_L is 1, 2 or 3-30 or 31 to 300 and A is $-CH_2CH_2O-$ or $-HNCH_2CO-$ or q_L is 1 and A is $C(O)-$ or $(CH_2)_{1-8}$ or q_L is 0, R_E is $-CH_2CH_2CH_2-$, q_L is 0 or q_L is 1 and A' is $-CH_2-$ and q_L is 0</p> <p>preferably</p> $O(CH_2CH_2O)_{q_L}CH_2CH_2NH_2, O(CH_2CH_2O)_{q_L}CH_2CH(CH_2NH_2)NH_2, OCH(CH_2NH_2)NH_2, CH(CH_2NH_2)NH_2, C(O)NH_2, -(CH_2)_{1-8} \text{ or } -(HNCH_2CO)_{1-3} (=gly_{1-3})-$		
<p>72 (withdrawn and currently amended). Kit comprising ligand precursors, linker precursors and tag precursors of formulae IV, IV', V, V' and/or VI as hereinbefore defined in Claim 59 for preparing a library of compounds of formula I $(Lig)_m L (J_T Tag)_m (J_L Lig)_m)_p$ and salts thereof wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers</p>	<p>[0181]</p> <p>[0173]</p> <p>[0114]</p>	

<p>comprising one or a plurality of same or different ligand moieties Lig each linked to one or a plurality of same or different tag moieties Tag via same or different linker moieties L and same or different linking site or linking functionality J_r and J_L</p> <p>wherein Lig comprises a GPCR ligand, an inhibitor of an intracellular enzyme or a substrate or inhibitor of a drug transporter;</p>	
<p>L is selected from a <u>single</u> or <u>double</u> bond, -O-, -S-, amine, COO-, amide, -NN-hydrazine; and saturated or unsaturated, substituted or unsubstituted C₁₋₆₀₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, wherein optional substituents are selected from any C₁₋₂₀ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano and carbonyl and combinations thereof, and L may be monomeric, oligomeric having oligomeric repeat of 2 to 30 or polymeric having polymeric repeat in excess of 30 up to 300;</p>	[0045]
<p>Tag is any tagging substrate;</p>	[0015]
<p>m are each independently selected from a whole number integer from 1 to 3;</p>	[0016]
<p>p is 0 to 3</p>	[0017]
<p>wherein one or more of each -Tag in one or more or each library compound is a fluorophore entity -Fl, whereby the library comprises compounds of which one or more or all of which <u>compounds</u> are of formula I'</p>	[0018]
<p>(LigI)_m L (J_rFl)_m (J_r L (J_LLig)_m)_p</p>	[0027]

<p>characterised in that wherein linking is at same or different linking sites in compounds comprising different Lig, J_L, L, J_r and/or – Tag and is at different linking sites in compounds comprising same Lig, J_L, L, J_r and/or – Tag</p> <p>with the proviso that when Lig is CGP12177 and L is 1,1,4,4-tetramethyl butylamine C(CH₃)₂(CH₂)₂C(CH₃)₂NH, Fl is not BODIPY@ Fl, or when L is C(CH₃)₂(CH₂)₂C(CH₃)₂NHCSNH then Fl is not FITC, eosin or erythrosin wherein the or each Fl is selected from a red, near ir or blue dye.</p>	[0018]	
	[0115]	
<p>73 (withdrawn and currently amended). A library of fluorescent ligands of formula I or I' or a kit comprising a compound thereof as hereinbefore defined in Claim 47 for visualising receptors or receptor binding, assessing pharmacological properties of the fluorescent ligand, in high throughput screening of novel chemical entities that bind to the target receptor, in inhibiting an</p>	[0182, lines 1-10]	

intracellular enzyme or inhibiting a drug transporter or a substrate of a drug transporter, in studying drug transport or drugs suitable for transport or in distinguishing healthy or diseased tissue.		
<p>74 (withdrawn and currently amended). A library of fluorescent ligands of formula I or I' or a kit comprising a compound thereof as hereinbefore defined in claim <u>47</u> or <u>64</u> for use in a method for receptor binding or inhibition, intracellular enzyme inhibition or drug transport or inhibition and visualisation comprising contacting to <u>the</u> library or a compound thereof as defined in claim 47 with a sample comprising live cell material comprising GPCRs, intracellular enzymes or drug transporters in manner to facilitate binding or inhibition thereof or transport thereby, and detecting changes in fluorescence or location thereof.</p>	[0183]	
<p>75. (withdrawn and currently amended). A library of fluorescent ligands of formula I or I' or a kit comprising a compound thereof for use as claimed in claim 74 wherein the library or compound thereof is a fluorescent ligand(s) which has affinity such that it binds permanently, semi-permanently or transiently and remains bound when unbound ligand is washed away.</p>	[0172, lines 5-8]	Pg. 42, lines 4-6
<p>76. (withdrawn and currently amended). A library of fluorescent ligands of formula I or I' or a kit comprising a compound thereof for use as claimed in claim 74 wherein detecting a change in fluorescence is by means of confocal microscopy or fluorescence correlation spectroscopy.</p>	[0182]	Pg.2, lines 1-2; pg. 50, lines 15-16 and pag. 51, lines 20-28

<p>77. (withdrawn and currently amended). A library of fluorescent ligands of formula I or I' or a kit comprising a compound thereof for use as claimed in claim 74 wherein the library or compound thereof comprises fluorescent ligand agonist(s) which maintains its binding affinity and functional activity or is an antagonist <u>which maintains its binding affinity on linking or when linked to fluorescent moiety Fl.</u></p>	<p>[0172, lines 1-5]</p>	<p>Pg. 42, lines 1-4</p>
<p>78. (withdrawn and currently amended). A kit comprising a library or a compound of formula I or I' as claimed in claim 47 <u>or 64</u> and a target therefor provided as cell derived material selected from a cell line, expressing a GPCR, intracellular enzyme or drug transporter, membrane containing these proteins derived from such a cell line, solubilised receptor, enzyme or drug transporter or GPCR array from that cell line.</p>	<p>[0204, lines 1-5] [0185, lines 3-6]</p>	
<p>79. (withdrawn). Kit as claimed in Claim 78 wherein the cell derived material is provided in one of three forms: (1) from cells expressing a green fluorescent protein tagged receptor, intracellular enzyme or drug transporter; (2) from cells expressing an epitope tag for a commercially available fluorescent antibody or (3) a wild-type protein for which a specific fluorescent antibody is also provided.</p>	<p>[0204, lines 5-end]</p>	

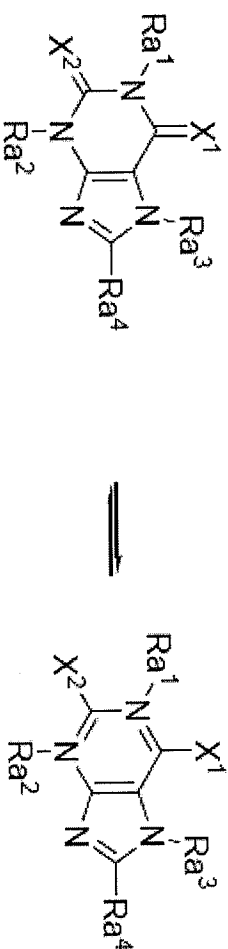
80-82. (canceled).		
<p>83. (withdrawn and currently amended). Library as claimed in Claim 59-55 comprising a plurality of compounds of the formula</p> <p style="text-align: center;">Lig₁-L₁-Fl</p> <p>wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers</p> <p>wherein Fl is selected from dyes in particular including fluorescein, fluorescein derivatives including FITC, and fluorescein-like molecules including Oregon Green™ and its derivatives, Texas red™, 7-nitrobenz-2-oxa-1,3-diazole (NBD) and derivatives thereof, coumarin and derivatives, naphthalene including derivatives of dansyl chloride or its analogues or derivatives, Cascade Blue™, EviBlue and fluorescent derivatives thereof, pyrenes and pyridyloxazole derivatives, the cyanine dyes, the dyes (DY dyes and ATO dyes) and fluorescent derivatives thereof, the Alexafluor dyes and derivatives, BDI dyes including the commercially available Bodipy™ dyes, erythrosin, eosin, pyrenes, anthracenes, acridines, fluorescent phycoobiliproteins and their conjugates and fluoresceinated microbeads, Rhodamine and fluorescent derivatives thereof including Rhodamine Green™ including the tetramethylrhodamines, X-rhodamines and Texas Red derivatives, and Rhodol Green™, coupled to amine groups using the isocyanate, succinimidy ester or dichlorotriazinyl reactive groups,</p>		

and

wherein $\text{Lig-J}_L\text{-J}_T$ is selected from the formulae Lig-a , Lig-b , Lig-c and Lig-d wherein:

Lig-a comprises linking functionality J_L which is amine, and is of the formula, in either of the following forms given:

Lig-a^1_m



wherein

Ra^4 comprises linking functionality J_L and J_T which is amine;

X^1 and X^2 are each O;

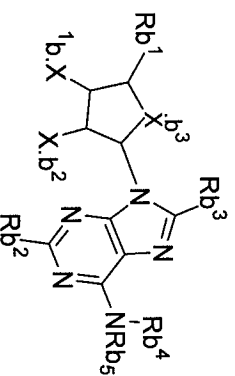
Ra^3 is H;

each of Ra^1 and Ra^2 is n-propyl;

Ra^4 is p-substituted phenyl wherein the substituent is heteroalkyl amide amine; and includes L which is a single bond or is C_{1-50} alkyl optionally substituted by C_1 alkyl and including

the formula $-(CH_2)_n$ where n is 3 to 8, optionally including one or more heteroatoms -O;

Lig.b comprises linking functionality J_L which is amine, and is



wherein ring substituents X.b¹ and X.b² are each OH;

ring heteroatom X.b³ is -O-;

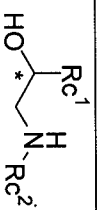
Rb¹ is CONHET or CH₂OH;

and each of R.b² and R.b³ is H;

Rb⁴ is H;

Rb⁵ comprises linking functionality J_r which is amino, and linker L.b selected from saturated C₁₋₁₂ aliphatic and C₆₋₂₄ aromatic, optionally substituted by one or more C₁ alkyl and optionally including one or more heteroatoms O or cyclic groups;

Lig.c comprises linking functionality J_L which is amine and is

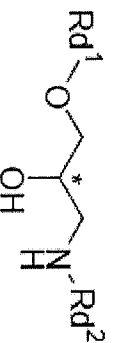


as a racemate or as one of its optically active isomers wherein * indicates an optically active centre,

Rc^1 is m-, p-dihydroxyphenyl; and

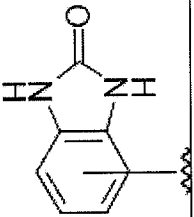
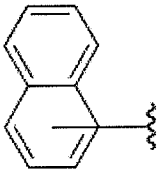
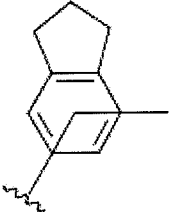
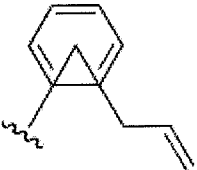
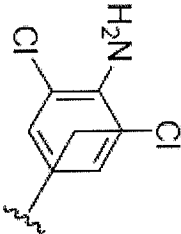
Rc^2 comprises linking functionality Jr which is amine, and linker Lc which is selected from C_{1-12} straight chain alkyl, C_{6-12} cycloalkyl or aryl and combinations thereof optionally comprising one or more heteroatoms O and optionally substituted by C_1 aliphatic;

or Lig.d comprises a linking functionality J_L which is amine and is



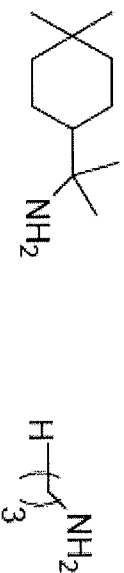
as a racemate or as one of its optically active isomers wherein * indicates an optically active centre,

Rd^1 is selected from the structures

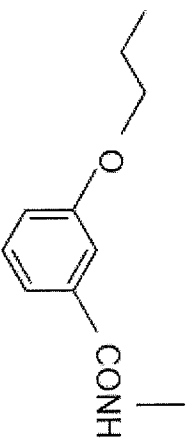
<p>and a substituted C₁₋₂₀ spiro aromatic ring system comprising a single aromatic ring and a heteroaryl and optionally halo substituted; and</p> <div style="display: flex; justify-content: space-around; align-items: center;">    </div> <div style="display: flex; justify-content: space-around; align-items: center;">   </div> <p>Rd² comprises linking functionality Jr which is amine, and linker L.d which is selected from C₁₋₁₂ straight chain alkyl, C₆₋₁₂ cycloalkyl or aryl and combinations thereof optionally comprising one or more heteroatoms O and optionally substituted by C₁ aliphatic; or Rd² is C₁₋₆ straight chain alkyl including ether O and substituted by C₆₋₁₀ aryl which is OH and oxo substituted and comprises linker L.d as hereinbefore defined.</p>		
<p>84. (withdrawn). Library as claimed in claim 83 wherein</p>		

R.a.⁴, R.b.⁵ or R.c.² or R.d.² comprises linking functionality J_r which is amino, and linker L.a, L.b, L.c or L.d selected from (CH₂)_m wherein m is 3, 4, 6 or 8 or is in the range 3 to 8 or 2 to 12 optionally including one or more substituents C₁, or J_L L J_r is mono or polyethylene glycol diamine, or L.a is a single bond; or

R.c.² or R.d.² comprises linking functionality J_r which is amino, and linker L.c or L.d selected from C(CH₃)₂CH₂Ph and mono amino menthane or the structure

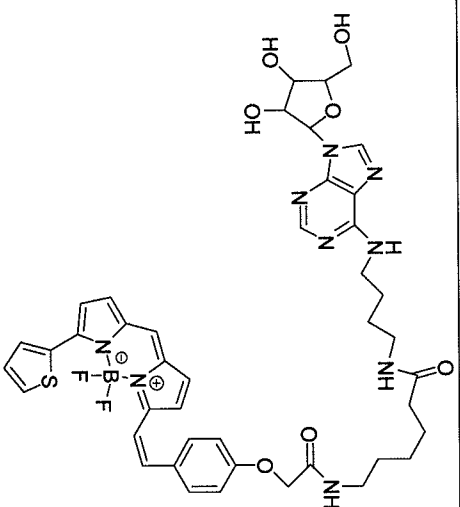


or R.d² comprises the following OH substituted aryl structure wherein linking functionality J_L is shown as amine, L.d is as hereinabove defined and includes J_r which is amine:

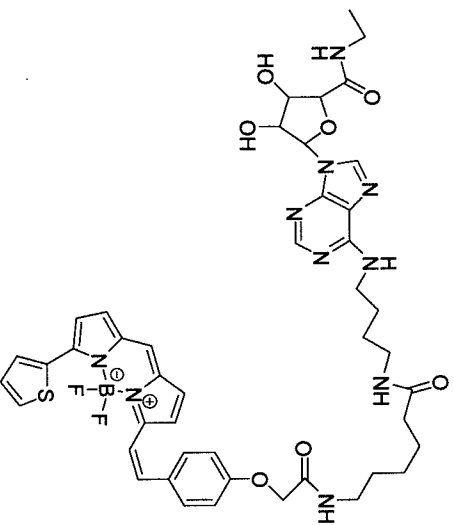


<p>85. (canceled).</p>		
<p>86. (withdrawn and currently amended). Library as claimed in Claim 83-47 wherein Fl is selected from <u>Texas Red™</u>, <u>Cy5.5</u> or <u>Cy5</u> or analogues thereof, <u>DY-630</u>, <u>DY-640</u>, <u>DY-650</u> or <u>DY-655</u> or analogues thereof, <u>ATTO 655</u> or <u>ATTO 680</u> or analogues thereof, <u>EvoBlue 30</u> or</p>	<p>[0117]</p>	

<p>analogues thereof, <u>Alexa 647</u> or analogues thereof, <u>BODIPY 630/650 X</u> and <u>analogues thereof</u> including <u>BODIPY 630/650 X</u>.</p>		
<p>87. (withdrawn and currently amended). Library as elaimed in claim 86 comprising a compound selected from the following structures wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers:</p> <div data-bbox="763 199 1006 1092" data-label="Chemical-Block"> </div> <p>XAC – BODIPY 630/650 X</p>	<p>[0219]</p>	<p>Pg. 59, lines 1-3</p>



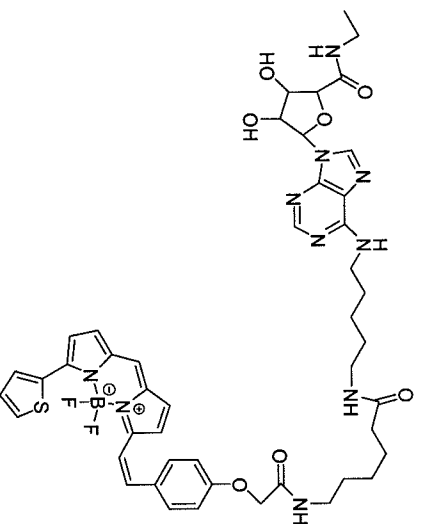
ABA-BY630



[0237]

Pg. 65, lines 1-3

ABEA-BY630



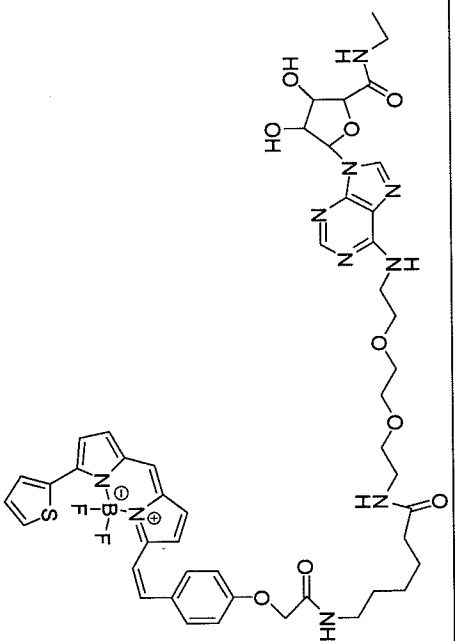
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[0239]

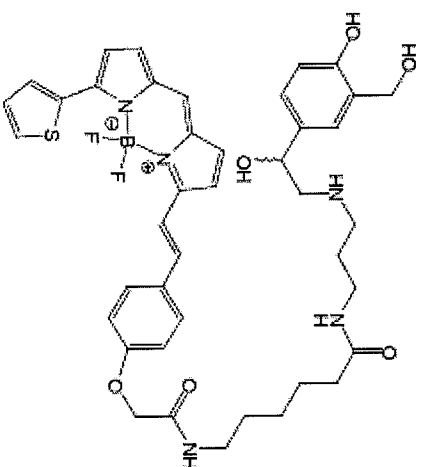
Pg. 66, lines 2-3

[0245]

Pg. 67; lines 1-3



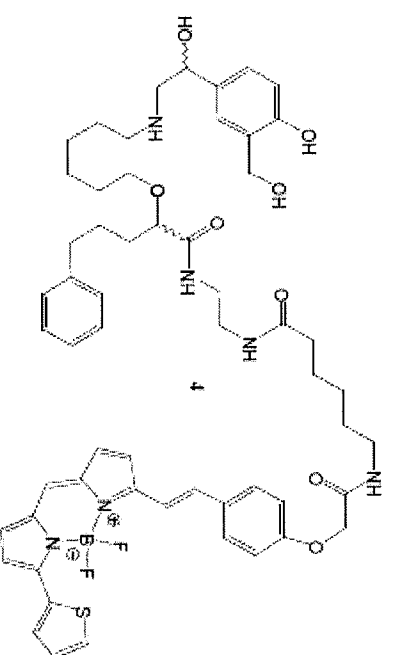
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And

Docket No. Q111431

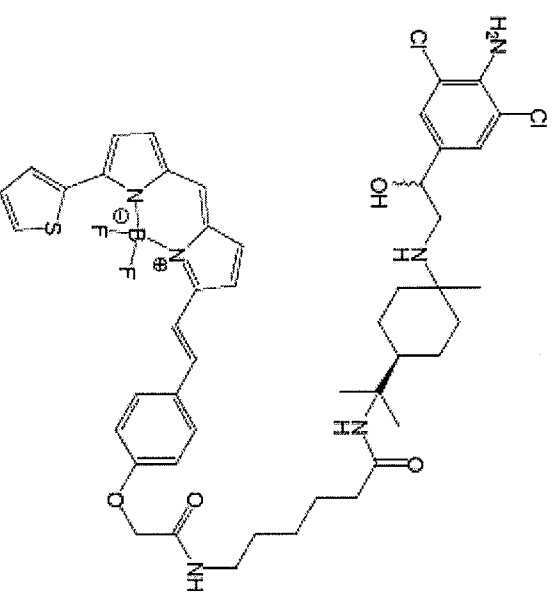
[0249]



[0249] &
[0250]

Pg. 68; scheme
4 and pg. 68,
lines 1-3

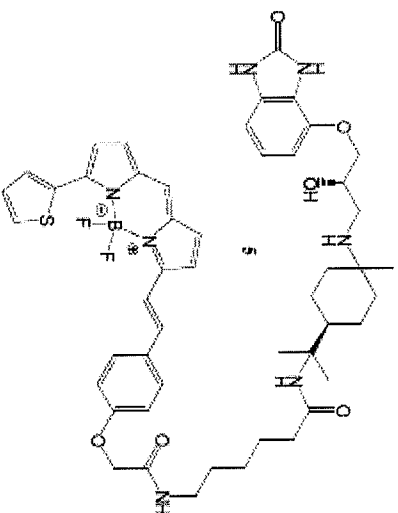
Salmeterol BY 630/650



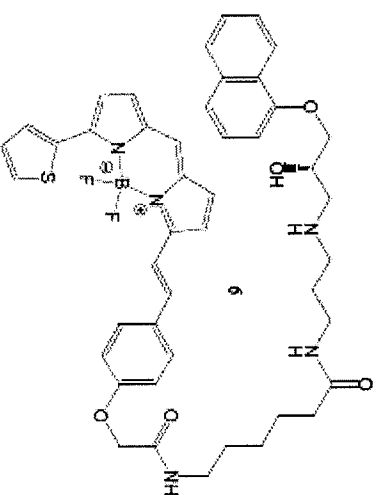
[0251]

Pg. 59, lines 15-
20

Clenbuterol BY 630/650

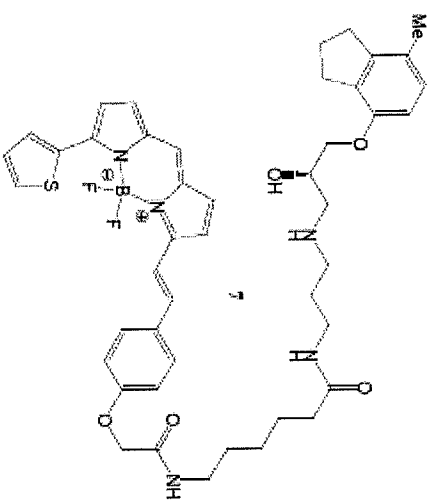


CGP12177-BY 630/650



Propranolol BY630/650

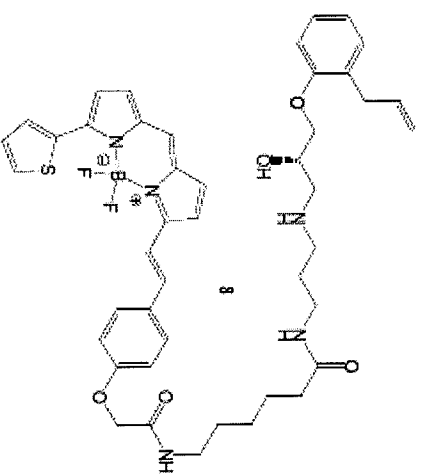
Docket No. Q111431



[252]

Pg. 70, line 10

ICI118551-BY630/650



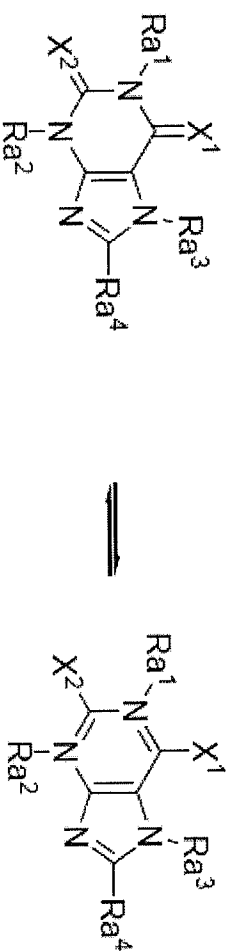
[0252]

Pg. 70, line 10

Alprenolol-BY630/650

88. (currently amended). Compound as claimed in Claim 67 of the formula $\text{Lig}^{\text{I}}-\text{L}^{\text{I}}-\text{Fl}$ wherein any optically active fluorescent ligand is present as a racemate or as one of its optically		

<p>active isomers</p> <p>wherein FI is selected from wherein FI is selected from dyes in particular including fluorescein, fluorescein derivatives including FITC, and fluorescein-like molecules including Oregon Green™ and its derivatives, Texas red™, 7-nitrobenz-2-oxa-1,3-diazole (NBD) and derivatives thereof, coumarin and derivatives, naphthalene including derivatives of dansyl chloride or its analogues or derivatives, Cascade Blue™, EyoBlue and fluorescent derivatives thereof, pyrenes and pyridyloxazole derivatives, the cyanine dyes, the dyomics (DY dyes and ATTO dyes) and fluorescent derivatives thereof, the Alexafluor dyes and derivatives, BDI dyes including the commercially available Bodipy™ dyes, erythrosin, eosin, pyrenes, anthracenes, acridines, fluorescent phycoobiliproteins and their conjugates and fluoresceinated microbeads, Rhodamine and fluorescent derivatives thereof including Rhodamine Green™ including the tetramethylrhodamines, X-rhodamines and Texas Red derivatives, and Rhodol Green™, coupled to amine groups using the isocyanate, succinimidyl ester or dichlorotriazinyl reactive groups; and</p> <p>wherein Lig J_L L_J is selected from the formulae Lig.a, Lig.b, Lig.c and Lig.d wherein:</p> <p>Lig.a comprises linking functionality J_L which is amine, and is of the formula, in either of the following forms given:</p> <p>Lig.a¹_m</p>	
--	--



wherein Ra^4 comprises linking functionality J_L and J_T which is amine;

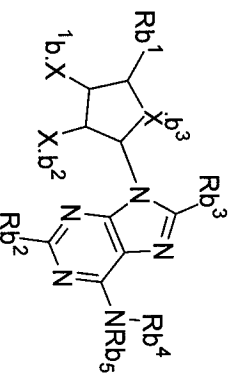
X^1 and X^2 are each O;

$R.a^3$ is H;

each of $R.a^1$ and $R.a^2$ is n-propyl;

$R.a^4$ is p-substituted phenyl wherein the substituent is heteroalkyl amide amine; and includes L which is a single bond or is C_{1-50} alkyl optionally substituted by C_1 alkyl and including the formula $-(CH_2)_n$ where n is 3 to 8, optionally including one or more heteroatoms -O;

Lig.b comprises linking functionality J_L which is amine; and is



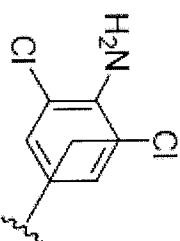
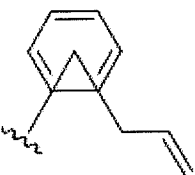
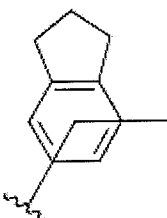
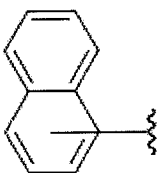
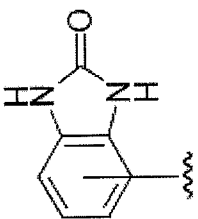
wherein ring substituents $X.b^1$ and $X.b^2$ are each OH;

ring heteroatom $X.b^3$ is -O-;

<p>Rb¹ is CONHEt or CH₂OH; and each of R.b² and R.b³ is H; Rb⁴ is H; Rb⁵ comprises linking functionality J_r which is amino, and linker L.b selected from saturated C₁₋₁₂ aliphatic and C₆₋₂₄ aromatic, optionally substituted by one or more C₁ alkyl and optionally including one or more heteroatoms O or cyclic groups;</p>	
<p>Lig.c comprises linking functionality J_L which is amine and is</p> <div data-bbox="906 199 1003 409" data-label="Chemical-Block"> </div> <p>as a racemate or as one of its optically active isomers wherein * indicates an optically active centre, Rc¹ is m-, p-dihydroxyphenyl; and Rc² comprises linking functionality J_r which is amine, and linker L.c which is selected from C₁₋₁₂ straight chain alkyl, C₆₋₁₂ cycloalkyl or aryl and combinations thereof optionally comprising one or more heteroatoms O and optionally substituted by C₁ aliphatic;</p>	
<p>or Lig.d comprises a linking functionality J_L which is amine and is</p> <div data-bbox="276 220 389 556" data-label="Chemical-Block"> </div>	

as a racemate or as one of its optically active isomers wherein * indicates an optically active centre,

Rd¹ is selected from the structures

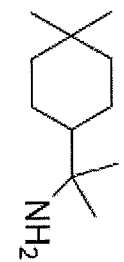


and a substituted C₁₋₂₀ spiro aromatic ring system comprising a single aromatic ring and a heteroaryl and optionally halo substituted; and

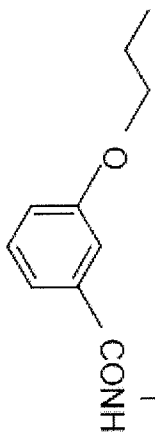
Rd² comprises linking functionality J_r which is amine, and linker L_d which is selected from C₁₋₁₂ straight chain alkyl, C₆₋₁₂ cycloalkyl or aryl and combinations thereof optionally comprising one or more heteroatoms O and optionally substituted by C₁ aliphatic; or Rd² is C₁₋₆ straight chain alkyl including ether O and substituted by C₆₋₁₀ aryl which is OH and oxo substituted and

comprises linker L.d as hereinbefore defined,
with the proviso that the compound is not a compound excluded in Claim 18.

89. (currently amended). Compound as claimed in Claim 88 wherein R.a.⁴, R.b.⁵ or R.c.² or R.d.² comprises linking functionality J_r which is amino, and linker L.a, L.b, L.c or L.d selected from (CH₂)_m wherein m is 3, 4, 6 or 8 or is in the range 3 to 8 or 2 to 12 optionally including one or more substituents C₁, or J_L L J_r is mono or polyethylene glycol diamine, or L.a is a single bond; or
R.c.² or R.d.² comprises linking functionality J_r which is amino, and linker L.c or L.d selected from C(CH₃)₂CH₂Ph and mono amino methane or the structure



or R.d.² comprises the following OH substituted aryl structure wherein linking functionality J_L is shown as amine, L.d is as hereinabove defined and includes J_r which is amine:



with the proviso that when ~~Lig~~ Lig is XAC ie in Lig.a when each of R.a¹ and R.a² is propyl, R.a³ is H and R.a⁴ is -Ph-OCH₂CONH(CH₂)₂NH-, and L is a single bond FI is not BODIPYTM 630/650 X; or

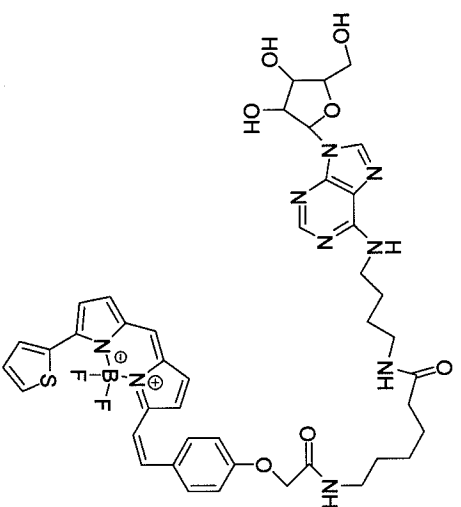
b) when Lig is ABEA, ie m is 4 and L is a single bond FI is not BODIPYTM 630/650 X.

90. (canceled)

91. (currently amended). Compound as claimed in Claim ~~88-64~~ wherein FI is selected from Texas RedTM, Cy5.5 or Cy5 or analogues thereof, DY-630, DY-640, DY-650 or DY-655 or analogues thereof, ATTO 655 or ATTO 680 or analogues thereof, EvoBlue 30 or analogues thereof, Alexa 647 or analogues thereof, BODIPY 630/650-X and analogues thereof including BODIPY 630/650-X.

[0117]

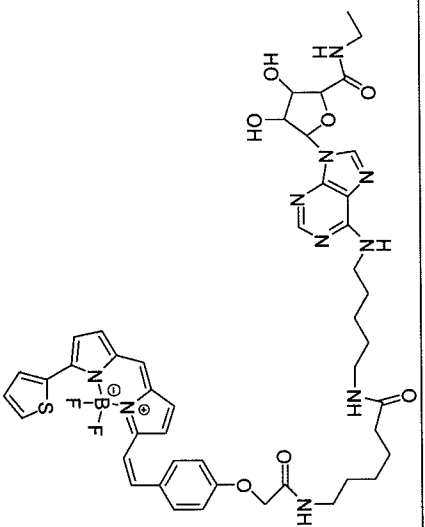
92. (withdrawn and currently amended). Compound selected from the structures wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers:



ABA-BY630

[0225]

Pg. 57, lines 1-3

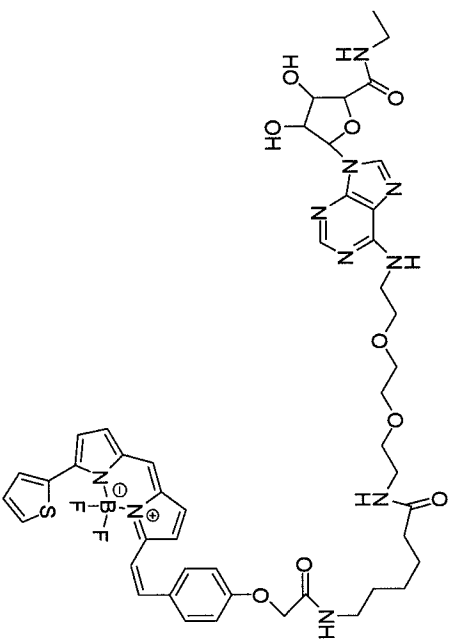


[0239]

Pg. 59, lines 1-3

[0245]

Pg. 67, lines 1-3

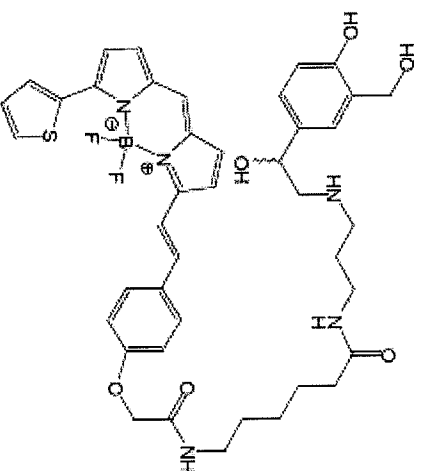


[0249]

Pg. 68, scheme
4

APPEA-BY 630

ABIPEA - BY630



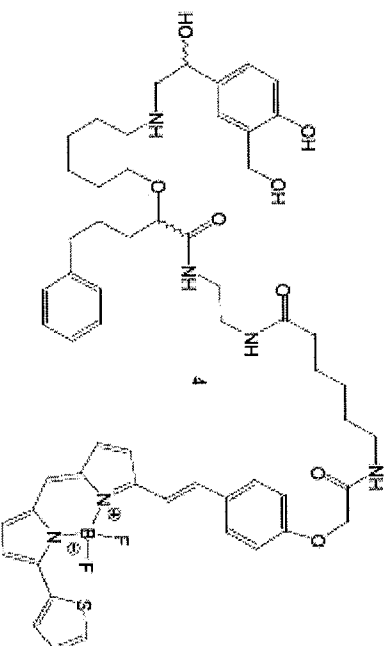
[0249]

Pg. 68; scheme

[0250]

4 and pg. 69,
lines 1-3

And Salmeterol derivative – BY 630/650



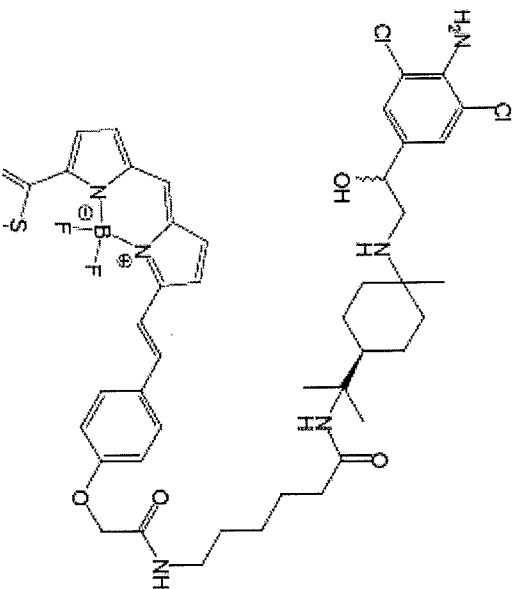
[251]

Pg. 69, lines 15-
20

[0252]

Pg. 70, line 5

Salmeterol BY 630/650



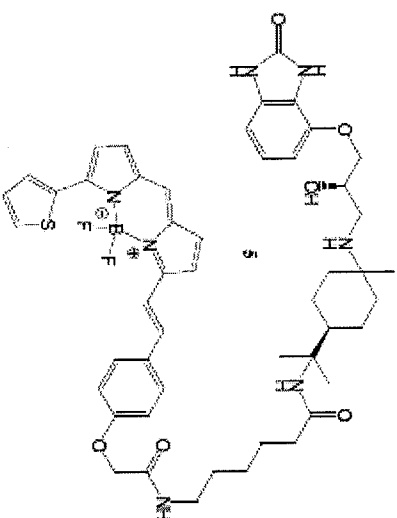
[0252]

Pg. 70, line 5

[0252]

Pg. 70, line 10

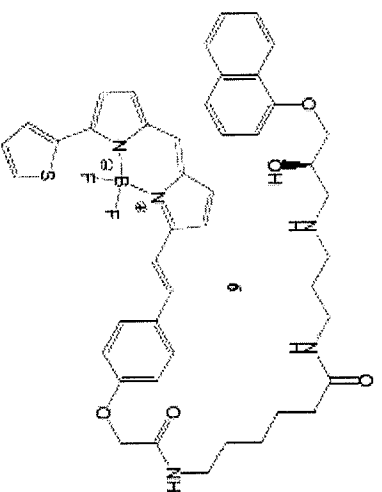
Clenbuterol BY 630/650



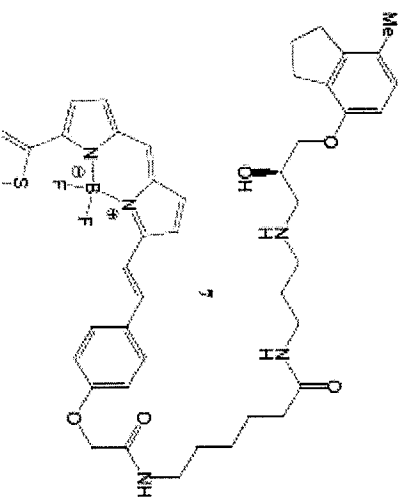
CGP12177-BY 630/650

[0252]

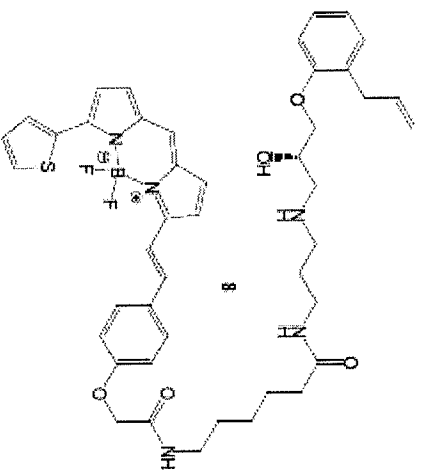
Docket No. Q111431



Propranolol BY630/650



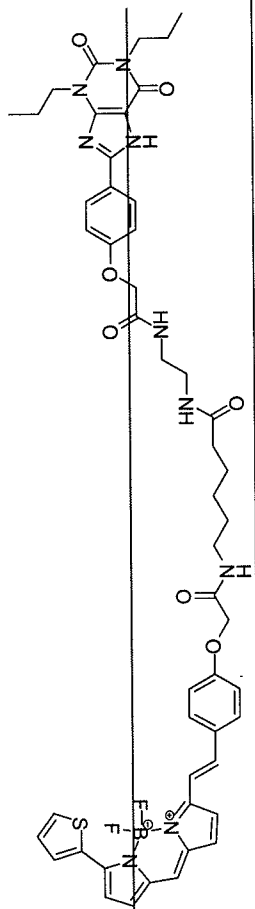
ICI118551-BY630/650



Alprenolol-BY630/650

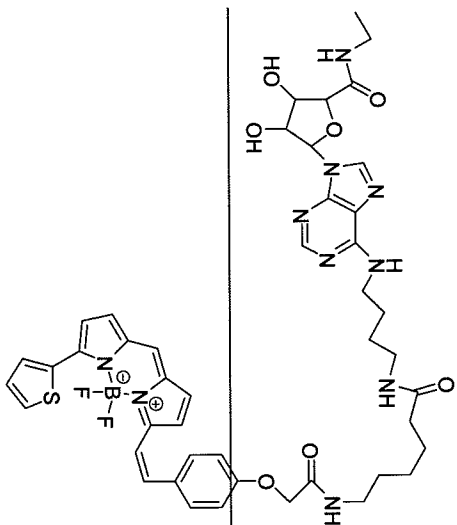
and optionally additionally

Docket No. Q111431



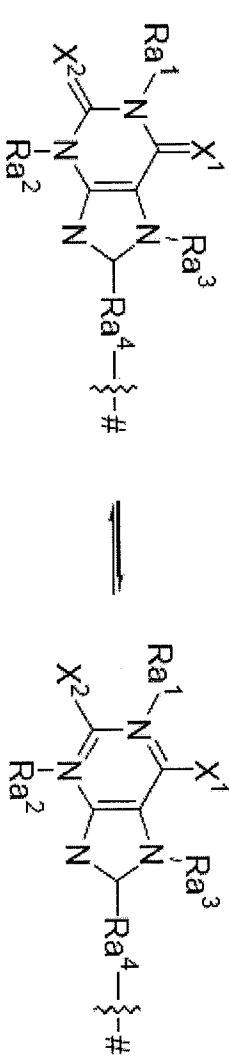
XAC-BODIPY-630/650-X

or



ABEA-BY630.

Docket No. Q111431

93. (new and withdrawn).	Library of tagged non-peptide ligands comprising moiety Lig and L selected from formula Lig.a-L.a- - Lig.e-L.e associated with a Tag which is an entity -FI wherein the or each -FI is selected from a red, near ir or blue dye and wherein: Lig.a- is suitably of the formula, in either of the following forms given:	
Lig.a ¹ -		<p>[0060] Pg. 16, line 16</p> <p>[0115] Pg. 27, line 27 (continuous)</p>
Wherein	<p>X¹ and X² are each independently selected from H, =O, OR.a, NR.a, NHR.a;</p> <p>X¹ and X² are each preferably =O;</p> <p>each of R.a, R.a¹, R.a² and R.a³ independently is selected from H or C₁₋₄ linear or branched alkyl, preferably H, methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl or isobutyl optionally mono or multi hydroxy or halo substituted, such as CH₂OH, CH₂F or CH₂CHOHCH₂OH;</p>	[0066]

R.a⁴ is selected from a heteroatom O, S or substituted or unsubstituted amine or saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like;

preferably

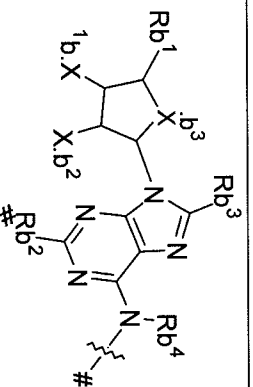
R.a⁴ is selected from optionally substituted aryl, cycloalkyl, alkyl, ketone, (di)amine, (di)amide, more preferably optionally substituted alkoxy, cycloalkyl, amine, amide, carboxylic acid or optionally o-, m- or p- substituted phenyl wherein substituents include aryl, alkyl, cycloalkyl, heteroaryl or heteroalkyl, amine, amide, carbonyl, carbonyl etc, for example is cyclohexyl, cyclopentyl, ethoxy, (CH₂)₂PhPh, CH₂Ph, CONH(CH₂)_nCONH, CH₂CONH(CH₂)₂NH, CH₂PhNHCOCH₂, CH₂CH₂OCOCH₂, succinimidyl ester, NHCOCH₂, CH₂(CH₃)NCOCH₂, H₂N(CH₂)₂NHCOCH₂, H₂N(CH₂)₈NHCOCH₂, H₂NNHCOCH₂, CH₂CONH(CH₂)₂NHCOCH₂, HOPhCH₂N(CH₂CH₃.HOAc)(CH₂)₂NHCOCH₂, heterocyclic-(CH₂)₄CONH(CH₂)₂NHCOCH₂, heterocyclic-NHCON(heterocyclic)COCH₂ and the like;

or Lig.a- is of the formula Lig.a²-

[0067]

	<p>[0069]</p> <p>[0070]</p> <p>[0071]</p>	
<p>wherein each of C_{A1} and C_{A2} is independently selected from aryl, heteroaryl, cycloalkyl and heterocyclic, more preferably from phenyl, or aryl containing 1 or 2 ring heteroatoms, or heterocyclic containing 1 ring heteroatom and/or 1 ring – C=C- group;</p>	<p>[0072]</p>	
<p>Each of up to seven R.a⁵ is a substituent of a ring carbon or a ring heteroatom and: is independently selected from H, halo, hydroxy, thiol, amine, COOH, hydrazine, cyano, saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, and wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like, such as =O, OCH₃, CH₂Ph(OCH₃)₂, O(CH₂)₃CON(CH₃)c_{hex},</p>	<p>[0073]</p>	

<p> $N(CH_2CH_2OH)_2$, c.hex, $COOCH_2CH_3$, CH_2CH_3; or any two or more of R.a⁵ form a one, two or three ring fused cyclic structure, preferably comprising a fused 3 ring aryl, 5-heterocyclic, 6-heterocyclic structure having 4 ring atoms common with the fused bicyclic Lig.a² structure; and R.a⁶ is a moiety as defined for R.a⁵ above; and -L.a- is as hereinbefore defined for -L- and is suitably of formula -L.I- or -L.II- as hereinbefore defined, more preferably is selected from a single bond, amino acid or amide such as a peptide or polypeptide for example gly or gly₃, alkyl of formula $-(CH_2)_n$ where n is 3 to 8, preferably 3, 4 or 6, optionally including one or more heteroatoms or unsaturated groups, such as -O- or -S- or $-CH=CH-$ and the like: </p> <p>Lig.b is suitably of the formula Lig.b</p>		
<p>Lig.b</p>	<p>[0075]</p> <p>[0076]</p> <p>[0077]</p>	



wherein ring substituents X.b¹ and X.b² are independently selected from hydrocarbon such as alkyl

or SR_X, NR_{X,2} and OR_X wherein (each) R_X is selected from H, C₁₋₃alkyl, alkenyl;

ring heteroatom X.b³ is selected from -S-, -O- and -CH₂-;

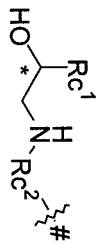
Rb¹ is selected from saturated or unsaturated, substituted or unsubstituted C₁₋₄ aliphatic, or C₁₋₃ alicyclic optionally including one or more heteroatoms N, O, S, P, wherein substituent(s) are selected from one or more cycloalkyl, heterocyclic, hydroxy, oxo, halo, amine; preferably R.b¹ comprises a carbonyl substituted by H, alkyl or a linear or cyclic primary, secondary or tertiary amine, substituted C₁₋₃ alkyl, cycloalkyl or amide, more preferably cyclopropyl, or CONHC₁₋₃alkyl such as CONHEt or CH₂OH

and each of R.b² and R.b³ is selected from H, halo, hydroxy, thiol, amine, COOH, CHO, hydrazine, cyano or saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or

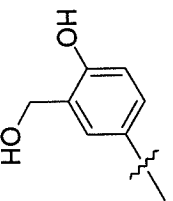
[0078]

[0079]

[0082]

<p>alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like, preferably from H, halo or hydroxy, preferably H or Cl;</p>	
<p>Rb⁴ is H; -L.b- is as hereinbefore defined for -L-, more preferably saturated and unsaturated substituted or unsubstituted C₁₋₁₂ aliphatic or C₁₋₂₄ aromatic as defined for -L- preferably including one or more heteroatoms O, S or N, cyclic or heterocyclic groups, more preferably is of formula -L.I- or -L.II- as hereinbefore defined, most preferably is -(CH₂)_m wherein m is 2 to 12, preferably 3, 4, 6 or 8, or is -(Ph-CH₂CONH)₂ (CH₂)₂-;</p>	<p>[0084] [0085]</p>
<p>Lig.c is suitably a non-peptide of the formula</p> <p>Lig.c HOC*(R.c¹)CH₂NH-R.c²-</p>	
<p></p> <p>Where * indicates an optically active centre and Wherein R.c¹ is C₆₋₁₄ aryl optionally including one or more heteroatoms selected from H, O,</p>	

optionally substituted by OH, Hal eg Cl, NH₂, NHC₁₋₃alkyl, sulphonamide, oxoamine (-CONH₂) and the like, more preferably mono, di or tri substituted phenyl or quinoline wherein substituents include OH, Cl or NH₂, more preferably m-CH₂OH, p-OH phenyl, m-,p-dihydroxy phenol or m-,m-dihydroxyphenol, m-,m-diCl, p-NH₂ phenol, p-OH, m-CONH₂ phenol or 5-OH, 8-quinoline and the like, such as



[0087]

R.c² is selected from saturated or unsaturated, substituted or unsubstituted C₁₋₂₀, preferably C₁₋₁₂, branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, wherein optional substituents are selected from any optionally substituted C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like and combinations thereof;

[0088]

Preferably R.c² is selected from C₁₋₆ branched or straight chain aliphatic, C₆₋₁₀ araliphatic optionally substituted by OH and optionally including heteroatoms selected from

N, O, preferably including an ether O, such as selected from $-(CH_2)-$
 $_6OCH((CH_2)_3Ph)$, $CHCH_3(CH_2)_2Ph$, $CHCH_3CH_2PhOH$, $C(CH_3)_2CH_2$;

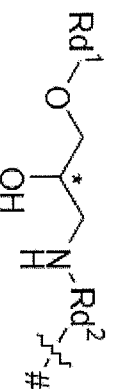
-L.c- is as hereinbefore defined for -L- and is suitably of formula -L.I- or -L.II- as
 hereinbefore defined, more preferably is selected from C_{1-12} alkyl, amide etc;

[0090]

Lig.d is suitably a non-peptide of the formula

[0091]

Lig.d $R.d^1 OCH_2C^*HOHCH_2NH-R.d^2- \#$



Where * indicates an optically active centre and where # indicates the site of linking to the
 fluorescent tagging moiety

Wherein $R.d^1$ is saturated or unsaturated, substituted or unsubstituted C_{1-20} branched or
 straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which
 may comprise one or more heteroatoms selected from N, O, S, P; wherein optional

substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like;

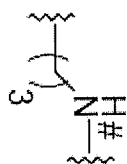
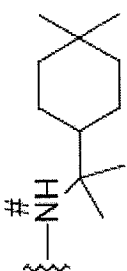
Preferably R.d¹ is substituted or unsubstituted C₁₋₂₄ aralkyl or heteroaralkyl, including single ring and fused ring systems with (hetero)aryl or cycloalkyl rings, wherein optional substituents include C₁₋₆ alkyl, alkoxy, ether, carbonyl, alkenyl, amine, amide each optionally carbonyl, amide, halo or OH substituted, or halo such as chloro or OH, preferably R.d¹ is unsubstituted or substituted alkyl, alkenyl, halo, amine, amide, carbonyl, ketone, ether substituted phenyl or naphthyl, illustrated as follows, most preferably mono-, di-, tri- or tetra substituted mono or polycyclic fused aryl or cycloaryl or heterocycloaryl such as phenyl, carbazole or structures shown below or spiro ring systems, most preferably mono-, di-, tri- or tetra alkoxyalkyl, alkoxyalkoxyalkyl or CF₃ substituted phenyl or unsubstituted or monosubstituted naphthalene or 5,6 ring systems most preferably of the structures:

[0093]

[0094]

[0094]

<div data-bbox="1247 239 1442 457" data-label="Chemical-Block"> </div> <div data-bbox="1268 602 1425 774" data-label="Chemical-Block"> </div> <div data-bbox="1263 926 1430 1144" data-label="Chemical-Block"> </div> <div data-bbox="964 411 1159 583" data-label="Chemical-Block"> </div> <div data-bbox="976 726 1154 963" data-label="Chemical-Block"> </div> <p data-bbox="331 386 805 1461"> $R.d^2$ is substituted or unsubstituted amine, saturated or unsaturated, substituted or unsubstituted C_{1-12} branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C_{1-12} aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like, more preferably amine, C_{1-6} branched or straight chain alkyl optionally including ether O, and optionally substituted by C_{6-10} aryl, for example of the formula: </p>	<div data-bbox="810 1476 847 1568" data-label="Text"> <p>[0096]</p> </div>
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[0097]

i.pr, i.bu, $\text{CH}_2\text{CH}_2\text{O}$ (m- CONH_2 , p-OH) phenol, $\text{CH}_2\text{CH}_2\text{O}$ (o- OCH_3 phenol

[0098]

-L.d- is as hereinbefore defined for -L- and is suitably of formula -L.I- or -L.II- as hereinbefore defined, more preferably is a single bond or is as hereinbefore defined for -L.a-;

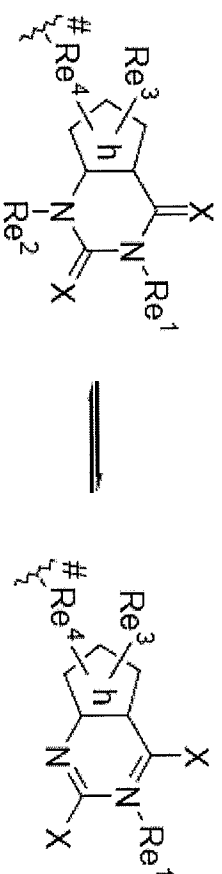
Lig.e

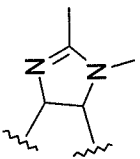
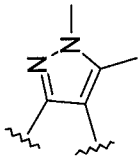
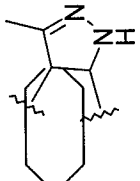
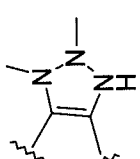
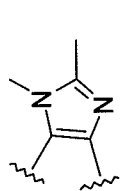
comprises a cell permeant moiety or is associated with a cell permeant L or Fl moiety and is suitably of the formula , in either of the following forms

given:

[0100]

Lig.e¹



wherein	h	is selected from
		[0102]
		[0103]
		[0104]
		
		
each optionally substituted by R.e ³ – R.e ⁴ wherein R.e ¹ – R.e ⁴ are as R.a ¹ – R.a ⁴ defined above or in which R.e ³ is C ₃₋₉ linear or branched alkyl, optionally mono or multi hydroxy or halo substituted or is aryl optionally substituted by alkoxy, sulfonyl and the like eg		
ortho-OEt, meta-SO ₂ N	NCH ₃	[0106]
each X is independently selected from H, =O, -OR.e ² , =N, HN, NR.e ⁵ , HR.e ⁶ , and		

<p>aryl optionally substituted by ether; or X is aryl optionally alkyl or alkoxy substituted such as Ph-ortho-OCH₂CH₂CH₃;</p>	<p>[0107] [0108]</p>	
<p>and where R.e⁵ is as defined above for R.e¹ above or forms a fused cyclic ring together with the adjacent ring N atom; preferably 1 or 2 fused 5 membered cyclic rings;</p>		
<p>and R.e⁶ is as defined above for R.e¹ above or is selected from optionally substituted phenyl wherein optional substituents include ether such as o-ethoxy or o-propoxy, alkyl, OH and the like, sulphonyl, carbonyl and the like substituted by heterocyclic, or cyclic C₅₋₈ alkyl such as methyl, piperazinyl, sulphonyl and the like;</p>	<p>[0109]</p>	
<p>or Lig.e is of the formula Lig.e²</p>	<p>[0110]</p>	
<p>Lig.e² (h) 5,6(h)</p> <p>Wherein each of C.E₁ and C.E₂ is independently selected from aryl, heteroaryl, cycloalkyl and heterocyclic, more preferably from phenyl, or aryl containing 1 or 2 ring heteroatoms, or heterocyclic containing 1 ring heteroatom and/or 1 ring – C=C- group;</p>	<p>[0111]</p>	

<p>Each of up to seven R.e¹¹ is a substituent of a ring carbon or a ring heteroatom and: is independently selected from saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, and wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like, such as =O, OCH₃, CH₂Ph(OCH₃)₂, O(CH₂)₃CON(CH₃)c.hex, N(CH₂CH₂OH)₂, c.hex, COOCH₂CH₃, CH₂CH₃; or any two or more of R.e¹¹ form a one, two or three ring fused cyclic structure, preferably comprising a fused 3 ring aryl, 5-heterocyclic, 6-heterocyclic structure having 4 ring atoms common with the fused bicyclic Lig.e³ structure; and R.e¹² is a moiety as defined for R.e¹¹ above;</p> <p>Preferably Lig.e is of the formula Lig.e¹ as hereinbefore defined in particular where R.e² and R.e³ are respectively propyl and butyl;</p> <p>-L.e- is suitably as hereinbefore defined for -L.a-</p>		
<p>94. (new and withdrawn). Library as claimed in claim 93 wherein the or each FI is selected</p>	<p>[0115]</p>	

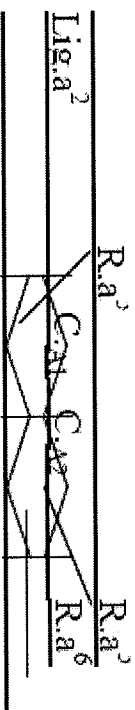
<p>from the following dyes: Texas red™, coumarin and derivatives, Cascade Blue™, EvoBlue and fluorescent derivatives thereof, pyrenes and pyridyloxazole derivatives, the cyanine dyes, the dyomics (DY dyes and ATTO dyes) and fluorescent derivatives thereof, the Alexafluor dyes and derivatives, BDI dyes including the commercially available Bodipy™ dyes, pyrenes, anthracenes, acridines, fluorescent phycobiliproteins and their conjugates and fluoresceinated microbeads, and Texas Red derivatives, coupled to amine groups using the isocyanate, succinimidyl ester or dichlorotriazinyl-reactive groups.</p>		
<p>95. (new): Compound which is a tagged non-peptide ligand comprising moiety Lig and L selected from formula Lig.a-L.a- - Lig.e-L.e associated with a Tag which is an entity -FI wherein -FI is selected from a red, near ir or blue dye and wherein:</p> <p>Lig.a- is suitably of the formula, in either of the following forms given:</p> <p>Lig.a¹-</p>	<p>[0060]</p> <p>[0115]</p> <p>[0061]</p> <p>[0063]</p> <p>[0064]</p>	

	[0065]	
<p>Wherein X^1 and X^2 are each independently selected from H, =O, OR.a, NR.a, NHR.a; X^1 and X^2 are each preferably =O;</p> <p>each of R.a, R.a¹, R.a² and R.a³ independently is selected from H or C₁₋₄ linear or branched alkyl, preferably H, methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl or isobutyl optionally mono or multi hydroxy or halo substituted, such as CH₂OH, CH₂F or CH₂CHOHCH₂OH;</p> <p>R.a⁴ is selected from a heteroatom O, S or substituted or unsubstituted amine or saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like;</p> <p>R.a⁴ is selected from optionally substituted aryl, cycloalkyl, alkyl, ketone, (di)amine, (di)amide, more preferably optionally substituted alkoxy, cycloalkyl, amine, amide, carboxylic acid or optionally o-, m- or p- substituted phenyl wherein</p>	[0066]	
<p>[0067]</p>	[0067]	

substituents include aryl, alkyl, cycloalkyl, heteroaryl or heteroalkyl, amine, amide, carboxyl, carbonyl etc, for example is cyclohexyl, cyclopentyl, ethoxy, $(\text{CH}_2)_2\text{PhPh}$, CH_2Ph , $\text{CONH}(\text{CH}_2)_n\text{CONH}$, $\text{CH}_2\text{CONH}(\text{CH}_2)_2\text{NH}$, $\text{CH}_2\text{PhNHCOCH}_2$, $\text{CH}_2\text{CH}_2\text{OCOCH}_2$, succinimidyl ester, NHCOCH_2 , $\text{CH}_2(\text{CH}_3)\text{NCOCH}_2$, $\text{H}_2\text{N}(\text{CH}_2)_2\text{NHCOCH}_2$, $\text{H}_2\text{N}(\text{CH}_2)_8\text{NHCOCH}_2$, $\text{H}_2\text{NNHCOCH}_2$, $\text{CH}_2\text{CONH}(\text{CH}_2)_2\text{NHCOCH}_2$, $\text{HOPhCH}_2\text{N}(\text{CH}_2\text{CH}_3.\text{HOAc})(\text{CH}_2)_2\text{NHCOCH}_2$, heterocyclic- $(\text{CH}_2)_4\text{CONH}(\text{CH}_2)_2\text{NHCOCH}_2$, heterocyclic-NHCON(heterocyclic) COCH_2 and the like;

[0069]

or Lig.a- is of the formula Lig.a²-



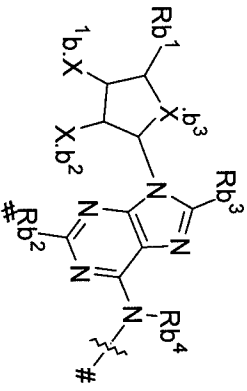
[0070]

[0071]

wherein each of C.A1 and C.A2 is independently selected from aryl, heteroaryl, cycloalkyl and heterocyclic, more preferably from phenyl, or aryl containing 1 or 2 ring heteroatoms, or heterocyclic containing 1 ring heteroatom and/or 1 ring - C=C- group;

Each of up to seven R.a⁵ is a substituent of a ring carbon or a ring heteroatom and: is independently selected from H, halo, hydroxy, thiol, amine, COOH, hydrazine, cyano, saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain

<p>aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, and wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like, such as =O, OCH₃, CH₂Ph(OCH₃)₂, O(CH₂)₃CON(CH₃)c.hex, N(CH₂CH₂OH)₂, c.hex, COOCH₂CH₃, CH₂CH₃;</p> <p>or any two or more of R.a⁵ form a one, two or three ring fused cyclic structure, preferably comprising a fused 3 ring aryl, 5-heterocyclic, 6-heterocyclic structure having 4 ring atoms common with the fused bicyclic Lig.a² structure;</p> <p>and R.a⁶ is a moiety as defined for R.a⁵ above;</p> <p>and -L.a- is as hereinbefore defined for -L- and is suitably of formula -L.I- or -L.II- as hereinbefore defined, more preferably is selected from a single bond, amino acid or amide such as a peptide or polypeptide for example gly or gly₃, alkyl of formula -(CH₂)_n where n is 3 to 8, preferably 3, 4 or 6, optionally including one or more heteroatoms or unsaturated groups, such as -O- or -S- or -CH=CH- and the like:</p> <p>Lig.b is suitably of the formula Lig.b</p>	<p>[0072]</p> <p>[0073]</p>	
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	[0075]	
<p>wherein ring substituents X.b¹ and X.b² are independently selected from hydrocarbon such as alkyl or SR_X, NR_{X.2} and OR_X wherein (each) R_X is selected from H, C₁₋₅alkyl, alkenyl;</p> <p>ring heteroatom X.b³ is selected from -S-, -O- and -CH₂-;</p>	[0076]	
<p>Rb¹ is selected from saturated or unsaturated, substituted or unsubstituted C₁₋₄ aliphatic, or C₁₋₃ alicyclic optionally including one or more heteroatoms N, O, S, P, wherein substituent(s) are selected from one or more cycloalkyl, heterocyclic, hydroxy, oxo, halo, amine; preferably R.b¹ comprises a carbonyl substituted by H, alkyl or a linear or cyclic primary, secondary or tertiary amine, substituted C₁₋₃ alkyl, cycloalkyl or amide, more preferably cyclopropyl, or CONHC₁₋₃alkyl such as CONHEt or CH₂OH</p>	[0077]	
<p>and each of R.b² and R.b³ is selected from H, halo, hydroxy, thiol, amine, COOH, CHO, hydrazine, cyano or saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P;</p>	[0078]	

wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like, preferably from H, halo or hydroxy, preferably H or Cl;

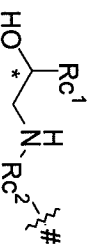
Rb⁴ is H;

-L.b- is as hereinbefore defined for -L-, more preferably saturated and unsaturated substituted or unsubstituted C₁₋₁₂ aliphatic or C₁₋₂₄ aromatic as defined for -L- [0079]
[0082]

preferably including one or more heteroatoms O, S or N, cyclic or heterocyclic groups, more preferably is of formula -L.I- or -L.II- as hereinbefore defined, most preferably is -(CH₂)_m wherein m is 2 to 12, preferably 3, 4, 6 or 8, or is -(Ph-CH₂CONH)₂ (CH₂)₂;

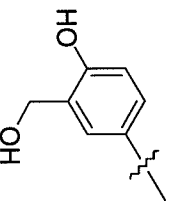
Lig.c is suitably a non-peptide of the formula

Lig.c HOC*(R.c¹)CH₂NH-R.c²-



Where * indicates an optically active centre and [0084]

Wherein R.c¹ is C₆₋₁₄ aryl optionally including one or more heteroatoms selected from H, O, optionally substituted by OH, Hal eg Cl, NH₂, NHC₁₋₃alkyl, sulphonamide, oxoamine (-CONH₂) and the like, more preferably mono, di or tri substituted phenyl or quinoline wherein substituents include OH, Cl or NH₂, more preferably m-CH₂OH, p-OH phenyl, m-,p-dihydroxy phenol or m-,m-dihydroxyphenol, m-,m-diCl, p-NH₂ phenol, p-OH, m-CONH₂ phenol or 5-OH, 8-quinoline and the like, such as

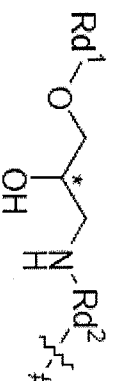


R.c² is selected from saturated or unsaturated, substituted or unsubstituted C₁₋₂₀, preferably C₁₋₁₂, branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any optionally substituted C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like and combinations thereof;

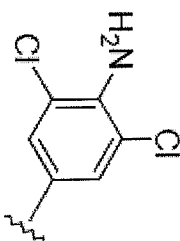
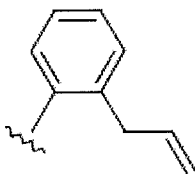
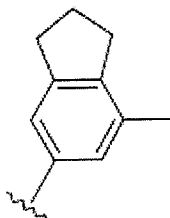
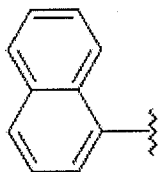
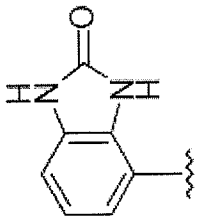
Preferably R.c² is selected from C₁₋₆ branched or straight chain aliphatic, C₆₋₁₀ araliphatic

[0085]

[0086]

<p>optionally substituted by OH and optionally including heteroatoms selected from N, O, preferably including an ether O, such as selected from $-(CH_2)-_6OCH((CH_2)_3Ph)$, $CHCH_3(CH_2)_2Ph$, $CHCH_3CH_2PhOH$, $C(CH_3)_2CH_2$;</p> <p>-L, c- is as hereinbefore defined for -L- and is suitably of formula -L.I- or -L.II- as hereinbefore defined, more preferably is selected from C₁₋₁₂ alkyl, amide etc;</p>	[0087]	
<p>Lig.d is suitably a non-peptide of the formula</p>	[0088]	
<p>Lig.d $R.d^1 OCH_2C^*HOHCH_2NH-R.d^2- \#$</p> 	[0090]	
<p>Where * indicates an optically active centre and where # indicates the site of linking to the fluorescent tagging moiety</p> <p>Wherein $R.d^1$ is saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional</p>	[0091]	

<p>substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like;</p> <p>Preferably R.d¹ is substituted or unsubstituted C₁₋₂₄ aralkyl or heteroaralkyl, including single ring and fused ring systems with (hetero)aryl or cycloalkyl rings, wherein optional substituents include C₁₋₆ alkyl, alkoxy, ether, carbonyl, alkenyl, amine, amide each optionally carbonyl, amide, halo or OH substituted, or halo such as chloro or OH, preferably R.d¹ is unsubstituted or substituted alkyl, alkenyl, halo, amine, amide, carbonyl, ketone, ether substituted phenyl or naphthyl, illustrated as follows, most preferably mono-, di-, tri- or tetra substituted mono or polycyclic fused aryl or cycloaryl or heterocycloaryl such as phenyl, carbazole or structures shown below or spiro ring systems, most preferably mono-, di-, tri- or tetra alkoxyalkyl, alkoxyalkoxyalkyl or CF₃ substituted phenyl or unsubstituted or monosubstituted naphthalene or 5,6 ring systems most preferably of the structures:</p>	<p>[0092]</p> <p>[0093]</p>
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[0094]

R.d²

is substituted or unsubstituted amine, saturated or unsaturated, substituted or unsubstituted C₁₋₁₂ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like, more preferably amine, C₁₋₆ branched or straight chain alkyl optionally including ether O, and optionally substituted by C₆₋₁₀ aryl, for example of the formula:

<div data-bbox="1312 205 1437 478" data-label="Chemical-Block"> </div> <div data-bbox="1312 625 1437 793" data-label="Chemical-Block"> </div> <p data-bbox="1141 380 1179 1346">i.pr, i.bu, CH₂CH₂O (m-CONH₂, p-OH) phenol, CH₂CH₂O (o-OCH₃ phenol</p> <p data-bbox="979 191 1068 1451">-L.d- is as hereinbefore defined for -L- and is suitably of formula -L.I- or -L.II- as hereinbefore defined, more preferably is a single bond or is as hereinbefore defined for -L.a-;</p> <p data-bbox="760 191 902 1451">Lig.e comprises a cell permeant moiety or is associated with a cell permeant L or FI moiety and is suitably of the formula , in either of the following forms given:</p>	<div data-bbox="1360 1476 1398 1560" data-label="Text">[0096]</div> <div data-bbox="540 1476 578 1560" data-label="Text">[0098]</div> <div data-bbox="760 1476 797 1560" data-label="Text">[0097]</div> <div data-bbox="321 1476 358 1560" data-label="Text">[0099]</div>
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Lig.e¹

<div data-bbox="1209 199 1429 1060" data-label="Chemical-Block"> </div> <div data-bbox="1039 189 1079 777" data-label="Text"> <p>wherein h is selected from</p> </div> <div data-bbox="609 388 966 955" data-label="Chemical-Block"> </div> <div data-bbox="267 378 487 1459" data-label="Text"> <p>each optionally substituted by $R.e^3 - R.e^4$ wherein $R.e^1 - R.e^4$ are as $R.a^1 - R.a^4$ defined above or in which $R.e^3$ is C_3-linear or branched alkyl, optionally mono or multi hydroxy or halo substituted or is aryl optionally substituted by alkoxy, sulfonyl and the like eg</p> </div>	<div data-bbox="1291 1470 1339 1564" data-label="Text"> <p>[01001]</p> </div> <div data-bbox="747 1470 795 1564" data-label="Text"> <p>[0102]</p> </div> <div data-bbox="633 1470 682 1564" data-label="Text"> <p>[0103]</p> </div> <div data-bbox="470 1470 519 1564" data-label="Text"> <p>[0104]</p> </div>
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1 N heteroatom and	5,6(h) comprises zero, 1 or 2 N	
<p>heteroatoms and is unsaturated or comprises one or two -C=C- or -C=N- groups; and wherein each ring is optionally substituted by one or more oxo, CO, COOH, C_{1-6} alkyl or linear or cyclic alkoxy such as methoxy, ethoxy or cyclopentyloxy optionally substituted by one or more oxo, CO, COOH, CN, or C_{1-6} alicyclic or amine groups, amine or one or more spiro or fused heterocycles;</p> <p>or Lig.e is of the formula Lig.e³</p> <div style="display: flex; justify-content: space-around; align-items: center; margin: 10px 0;"> <div style="text-align: center;"> R.e^{11} C.E1 </div> <div style="text-align: center;"> C.E2 </div> <div style="text-align: center;"> R.e^{11} R.e^{12} </div> </div> <p>Lig.e³</p> <p>Wherein each of C.E1 and C.E2 is independently selected from aryl, heteroaryl, cycloalkyl and heterocyclic, more preferably from phenyl, or aryl containing 1 or 2 ring heteroatoms, or heterocyclic containing 1 ring heteroatom and/or 1 ring -C=C- group;</p> <p>Each of up to seven R.e¹¹ is a substituent of a ring carbon or a ring heteroatom and: is independently selected from saturated or unsaturated, substituted or unsubstituted C_{1-20} branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of</p>		

<p>which may comprise one or more heteroatoms selected from N, O, S, P, and wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like, such as =O, OCH₃, CH₂Ph(OCH₃)₂, O(CH₂)₃CON(CH₃)c.hex, N(CH₂CH₂OH)₂, c.hex, COOCH₂CH₃, CH₂CH₃;</p> <p>or any two or more of R.e¹¹ form a one, two or three ring fused cyclic structure, preferably comprising a fused 3 ring aryl, 5-heterocyclic, 6-heterocyclic structure having 4 ring atoms common with the fused bicyclic Lig.e³ structure;</p> <p>and R.e¹² is a moiety as defined for R.e¹¹ above;</p> <p>Preferably Lig.e is of the formula Lig.e¹ as hereinbefore defined in particular where R.e² and R.e³ are respectively propyl and butyl;</p> <p>-L.e- is suitably as hereinbefore defined for -L.a-.</p>		
<p>96. (new). Compound as claimed in claim 95 wherein Fl is selected from the following dyes: Texas red™, coumarin and derivatives, Cascade Blue™, EvoBlue and fluorescent derivatives thereof, pyrenes and pyridyloxazole derivatives, the cyanine dyes, the dyomics (DY dyes and ATTO dyes) and fluorescent derivatives thereof, the Alexafluor dyes and derivatives, BDI dyes</p>	[0115]	

including the commercially available Bodipy™ dyes, pyrenes, anthracenes, acridines, fluorescent phycobiliproteins and their conjugates and fluoresceinated microbeads, and Texas Red derivatives, coupled to amine groups using the isocyanate, succinimidyl ester or dichlorotriazinyl-reactive groups.		
97 (new and withdrawn). Process for the preparation of a library as claimed in Claim 59, wherein reactive groups Y_{Lig} , Y_L , Y_T have suitable reactive group functionalities for linking by addition or addition – elimination reaction.	[0134]	
98 (new and withdrawn). Process for the preparation of a compound as claimed in Claim 60, wherein reactive groups Y_{Lig} , Y_L , Y_T have suitable reactive group functionalities for linking by addition or addition – elimination reaction.	[0134]	